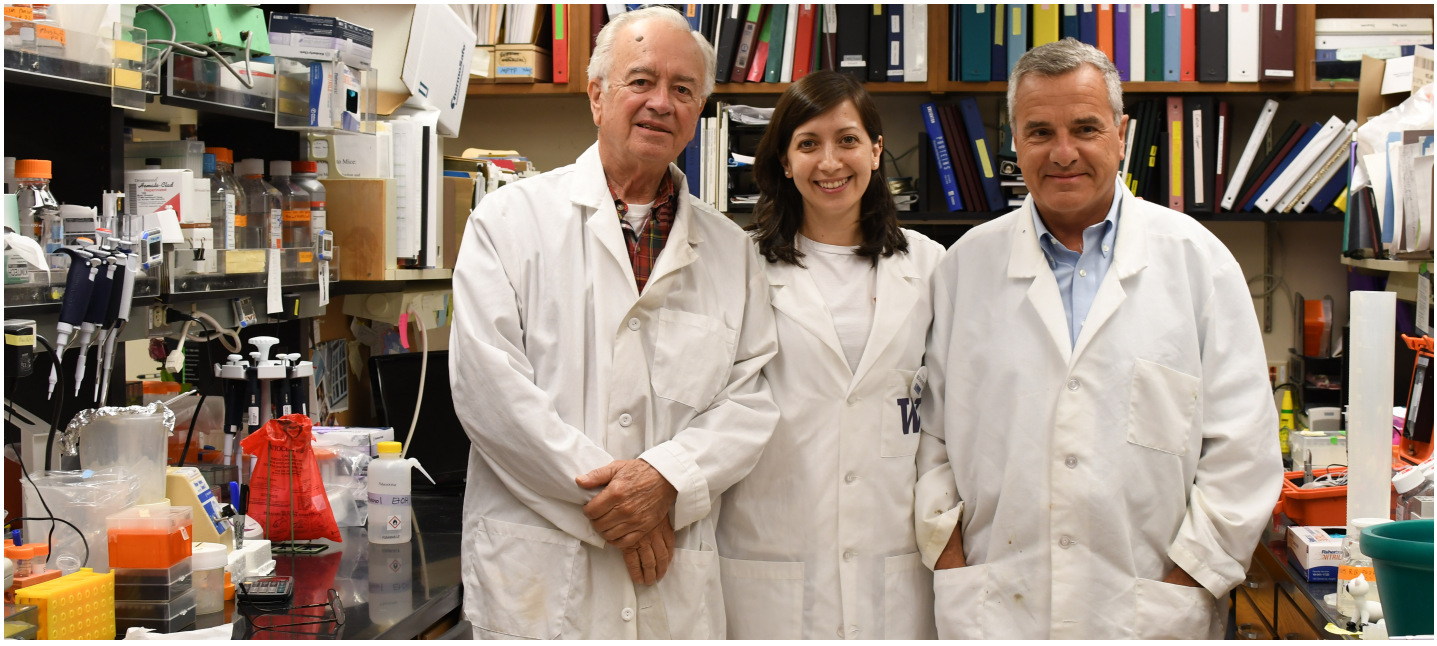
The Body's Defenses Against Heavy Metals

SUPERFUND RESEARCH PROGRAM
ENVIRONMENTAL & OCCUPATIONAL HEALTH SCIENCES

Understanding the protective role of two proteins

Not every person will respond to contaminant exposures in the same way. In part their response will be dictated by the levels of protective enzymes that they produce.

A person's response to contaminants is determined to a large extent by their genes. Dr. Clement Furlong, Dr. Lucio Costa and Dr. Judit Marsillach are pioneers in the study of two proteins that protect against the toxic effects of contaminants. These proteins are known as paraoxonases 1 and 2 (PON1 and PON2). PON1 is found in the liver and in blood, while PON2 is found in several tissues including the brain. Both are produced at different levels depending on genes, sex, age, and diet. People who make low levels of these protective enzymes are more likely to suffer damage to their nervous system from exposure to metals like manganese and cadmium or to certain pesticides.



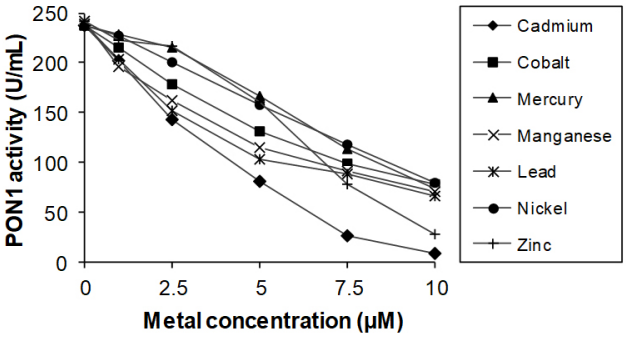
From left to right Dr. Clement Furlong, Dr. Judit Marsillach, and Dr. Lucio Costa pose in the Furlong lab.

PON1 and Human Health

So far, expression of PON1 in humans has been well-studied and is linked to increased sensitivity to certain pesticides. Lab studies have shown that mice lacking the *Pon1* gene die after exposure to a low level of organophosphate pesticide that does not affect survival of normal mice. When these mice lacking PON1 were given PON1 from an outside source they survived exposure to the pesticides. This is important to human health because some adults and all children under the age of two have very low levels of PON1. Recently, scientists have also found a potential role of PON1 in Parkinson's disease and other neurodegenerative diseases.

Understanding PON2

PON2 has been less studied than PON1 but is thought to be an important antioxidant and anti-inflammatory enzyme involved in determining a person's reaction to heavy metal exposure. As PON2 is produced in the brain, it may play an important role in protecting brain cells from damage. Drs. Furlong, Costa and Marsillach have shown that mice with low levels of *Pon2* are more sensitive to the oxidative stress caused by exposure to various heavy metals than normal mice. The research group has also shown that levels of PON2 can be influenced by sex (females produce more PON2 than males), environmental factors, and diet. PON2 has also been shown to protect PON1 against oxidative stress. All this could have important implications for human health. Currently Drs. Furlong, Marsillach and Costa are working to create an external source of PON2 that can be given to mice with low levels of PON2 to test whether outside sources of PON2 can reduce oxidative stress caused by exposure to heavy metals such as cadmium or manganese.



As the levels of heavy metals increase (along the x-axis) levels of PON1 activity decrease. Figure provided by Judit Marsillach.

Cadmium

Cadmium is a natural metal found in the Earth's crust known to cause cancer and impair learning. Most cadmium used in the United States is extracted during the production of other metals like zinc, lead and copper. Cadmium has many uses including in batteries, pigments, metal coatings, and plastics. The primary source of cadmium exposure is through smoking cigarettes. Smoking approximately doubles the levels of cadmium in the body compared to not smoking. Elevated cadmium levels can also be found in water sources like the Duwamish River near historical and current industries. Aquatic organisms will accumulate cadmium, potentially allowing it to enter the food supply. People who fish in local waters should be cautious and abide by any fish advisories. *Information provided by ATSDR*

THE UW SUPERFUND RESEARCH PROGRAM

The University of Washington Superfund Research Program is an interdisciplinary program that conducts and communicates research on the impacts of metal neurotoxicity on human and ecological health. Our research focuses on metals that commonly occur at Superfund hazardous waste sites for which there is incomplete understanding of their neurotoxic effects on human and ecological health. The physiological processes we study include adverse effects on cognition, olfaction, and neurobehavioral processes, and are associated with the risk of developing Alzheimer's and dementia, Parkinson's disease and other neurodegenerative diseases.

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