

Project 2 Zn Reversal of U Toxicity

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This project will leverage on an existing birth cohort study examining the reproductive and developmental outcomes from uranium (U) exposures on the Navajo Nation. It responds to repeated community requests that research not just identify problems, but develop solutions. Here, we merge a substantial body of mechanistic research on the potential of zinc to reverse toxicity of metals with the community-based cohort study to evaluate an intervention informed by laboratory studies, consistent with Navajo culture and traditional medicine, and potentially protective against the toxicity of U.

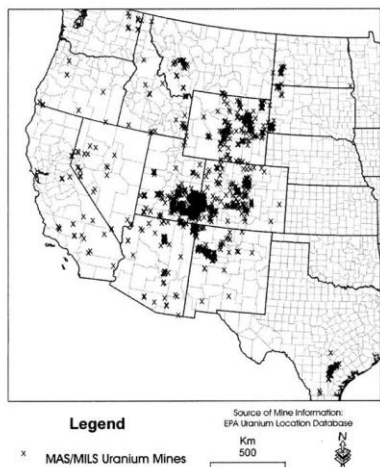
Aim #1: Through mentorship of a student from the Navajo community, examine a plausible mechanism for U-inhibition of DNA and its reversal of dietary zinc (Zn).

Aim #2: Test the hypothesis that U exposure will decrease repair of DNA and that supplemental Zn will ameliorate this adverse effect of U in an at-risk human population.

The Uranium Legacy of the Western U.S.

- USEPA estimates about 10,400 abandoned uranium "mine features" in 15 western states
- U.S. Bureau of Mines estimates ~4,100 discrete uranium mines

Source: <http://www.epa.gov/rpdweb00/t/enorm/uranium.html>



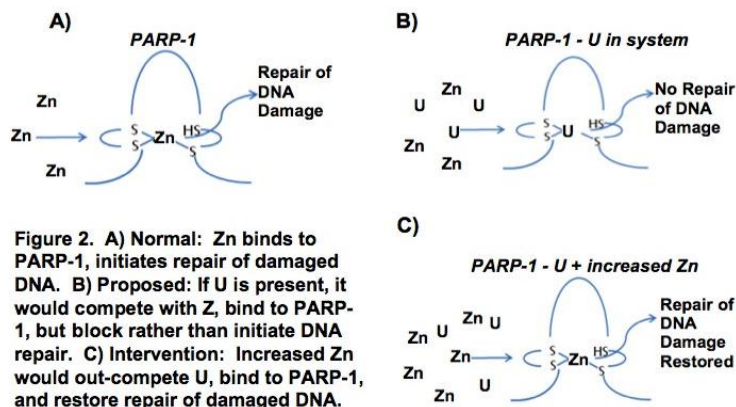
Native American women have disparately elevated rates of key reproductive health indicators and birth outcomes. Because of their traditions of living close to the land, Native Americans can have increased exposures to environmental contaminants. The location of many contaminated waste sites on Native lands has led to environmental injustices that can also increase the likelihood of exposures. On the Navajo Nation, more than 50 years of uranium mining and milling have resulted in more than 1100 unremediated waste sites, leading to concerns about exposures and the potential impact on reproductive and developmental outcomes in these communities. The map indicates this problem is not unique to Navajo, but has application through the rural and often Native communities in the Western US that have been affected by mining.

Aim 1 approach:

Mechanistic studies – Laboratory studies mentoring a Navajo chemistry student from these communities will investigate whether U disrupts the functions of a relevant DNA repair protein (PARP-1) and if Zn at concentrations found in prenatal vitamin supplements can restore PARP activity.

U binding to PARP-1: U binding to peptides representing an authentic PARP-1 Zn finger (PARPzf) will be analyzed using methods developed in Dr. Hudson's lab to examine As binding.

U alteration of PARPzf function: The functional relevance of U-Zn interactions with PARP will be evaluated in an actual PARP protein model developed in Dr. Hudson's laboratory in her work on As-Zn-PARP interactions.



Aim 2 approach:

Evaluation of a culturally appropriate intervention to restore the imbalance resulting from exposures to wastes.

- The use of a naturally occurring mineral such as zinc to restore the imbalance created by the extraction and

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dumping of uranium and associated wastes is consistent with traditional thinking about healing in Navajo communities.

- Zinc is routinely prescribed in a prenatal vitamin supplement in some IHS service units, but pharmacists report only about 50% compliance in use of these vitamins.
- By analyzing zinc in serum of participants in the highest and lowest quartiles of confirmed uranium exposures, we have a model to compare DNA repair relative to the observed uranium and zinc levels of participants.
- Data analysis – Data will be analyzed as a 2x2 factorial design with Zn and U as main effects, plus analysis of Zn-U interaction. Urine U and blood Zn will be used to assign categories for final analysis, but the correlations between predicted and observed U and Zn will be calculated to allow determination of sufficiency of the survey screen, geospatial, and pharmacists supplied data on compliance to inform their intervention.

Potential Community Benefits:

The results of this study will inform a possible intervention that is readily implemented, consistent with Navajo beliefs and practices, and responsive to community concerns. The work will build research expertise among Navajo community members and agencies participating in the parent birth cohort study, and also provide updated information on nutritional status in pregnancy.