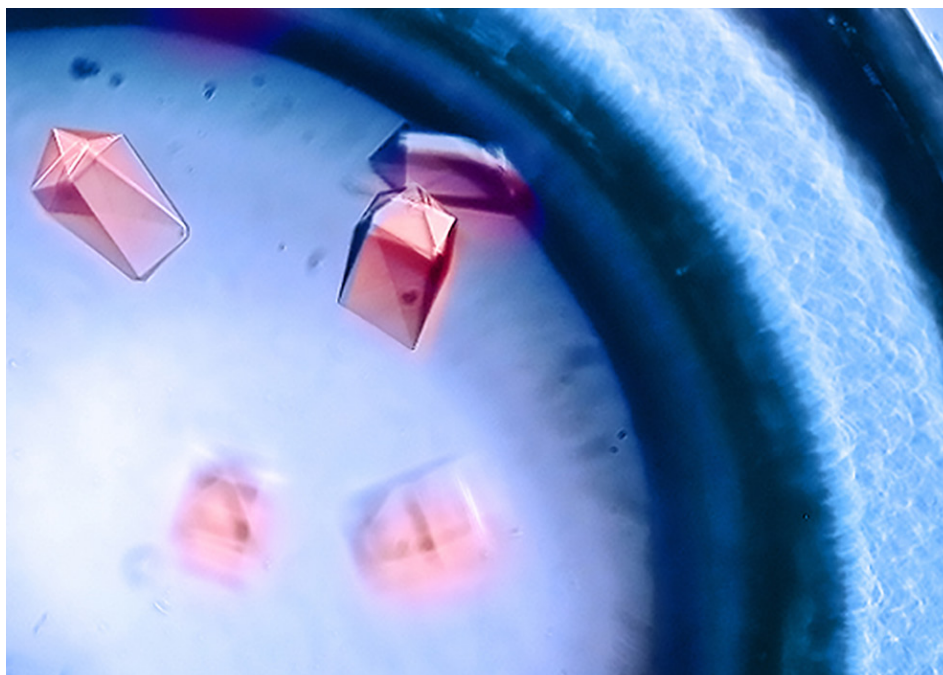
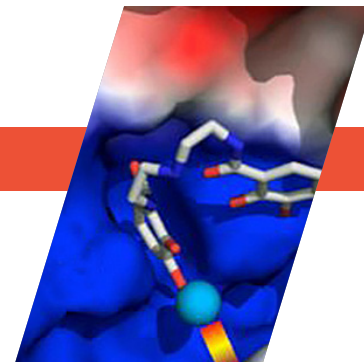


A New Pathway for Radionuclide Uptake



Crystals formed with the protein siderocalin and curium complexes exhibit bright red luminescence when exposed to UV light.

Synthetic radionuclides, such as the transuranic actinides plutonium, americium, and curium, present severe health threats as contaminants, and understanding the scope of the biochemical interactions involved in actinide uptake into cells is instrumental in managing human contamination. Recently, scientists have reported that an iron-binding protein called siderocalin can also bind and transport actinides into cells, a major advance in understanding the biological chemistry of radioactive metals. The research, which included structural biology studies at the ALS, opens up new avenues of research into strategies for remedial action in the event of possible human exposure to nuclear contaminants.

The research group, from Berkeley Lab and the Fred Hutchinson Cancer Research

Center, has already developed a compound to sequester actinides and expel them from the body. They have put it in a pill form that can be taken orally, a necessity in the event of radiation exposure amongst a large population. Last year, the FDA approved a clinical trial to test the safety of the drug, and they are seeking funding for the tests. However, a basic understanding of how actinides act in the body is still needed. Although actinides are known to rapidly circulate and deposit into major organs such as bone, liver, or kidney after contamination, the specific molecular mechanisms associated with mammalian uptake of these toxic heavy elements remain largely unexplored.

Typically, the mechanisms proposed for mammalian actinide transport have involved proteins that bind their targets

Biochemical Countermeasures

The release of actinides into the environment, particularly after a nuclear power plant accident or the potential use of a radiological dispersal device, is a public health threat. The actinides are all highly radioactive, as are some lanthanide fission products, and many of their isotopes decay by alpha-particle emission, a highly ionizing (and thus damaging) form of radiation. However, because alpha particles are not highly penetrating, their health effects appear only when they are inhaled, ingested, or otherwise internalized.

The damage and risk from such hazardous materials incorporated in the body can be mitigated by “decorporating” them—chemically removing them from the body. However, the biological chemistry of actinide metal ions is largely unknown, and new approaches to the understanding of pathways underlying contamination are needed. This work by Allred et al. identifies a new mammalian pathway for the intracellular delivery of the radioactive toxic metal ions that are actinides, through the protein siderocalin. Spectroscopic tools, including x-ray diffraction and luminescence, provided insights on the bonding characteristics of these metal ions, which is crucial to devising new strategies for decontamination.

directly. Siderocalin, an essential antibacterial protein that sequesters iron, binds indirectly, through tight complexes with a chelator (a molecule that forms multiple bonds with a metal ion). The researchers hypothesized that the metal ion could be

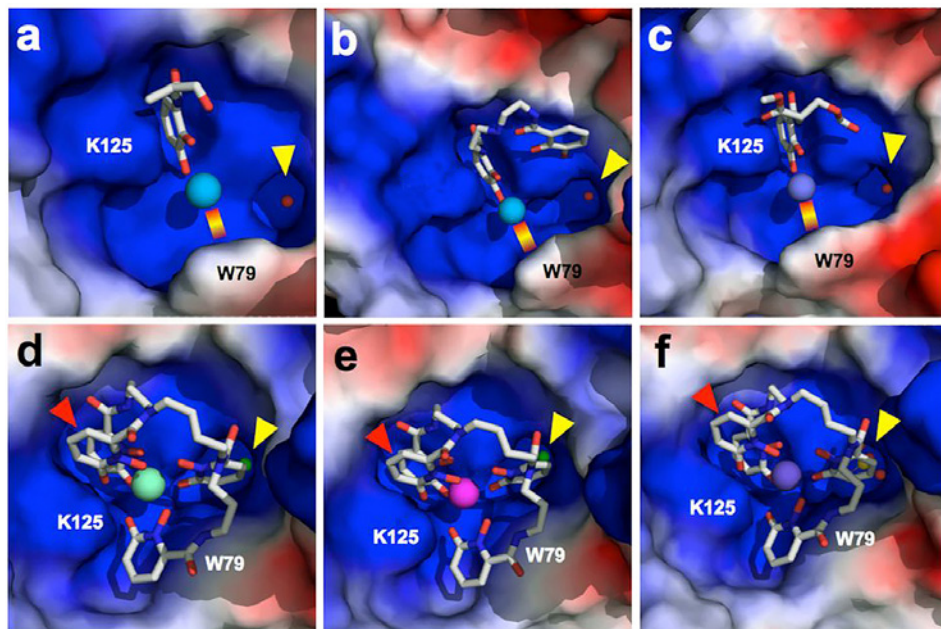
substituted without significantly affecting recognition, potentially uncovering cellular trafficking pathways for other elements or enabling novel applications.

At Beamlines 5.0.1 and 5.0.2, the team used crystallography to characterize complexes of siderocalin and transuranic actinides. The results confirmed specific binding, uncovered the details of protein-ligand and chelator-metal coordination, and highlighted differences in the recognition of nontransition metals with natural or synthetic chelators. These are the first protein structures containing thorium or the transuranic elements plutonium, americium, or curium. Until this work, there were no structures in the Protein Data Bank with those elements. The scientists also used cultured kidney cells to demonstrate the role of siderocalin in facilitating the uptake of the metal ions in cells.

By revealing a new pathway for the intracellular delivery of the radioactive toxic metal ions, the results could help scientists to develop new strategies to counteract actinide exposure. For example, instead of binding and expelling radionuclides from the body, one could possibly block the uptake.

The researchers also made the unexpected finding that siderocalin can act as a “synergistic antenna” that sensitizes the luminescence of actinides and lanthanides. They showed that adding the protein enhances the sensitization pathways, making it much brighter. This is a new mechanism that hasn’t yet been explored and could be very useful; it could have applications down the line for diagnostics and bioimaging.

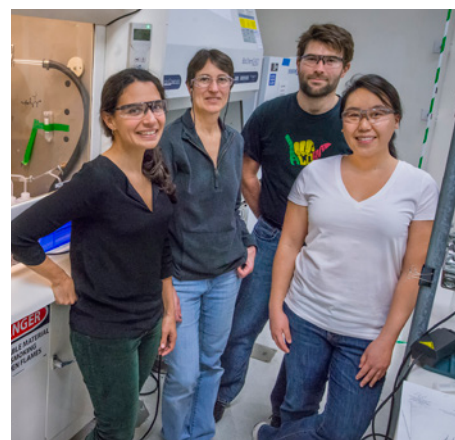
The researchers note that a study like this would have been possible in very few other places. Very few facilities have the capability to combine the different approaches and techniques—the spectroscopy techniques at the ALS, the ability to handle heavy elements that are radioactive, plus the chemical and biological tools available onsite. Beyond elucidating contamination pathways, these results also highlight new potential uses of siderocalin, ranging from the design of photoluminescent materials, to the separation of lanthanides and actinides in the nuclear fuel process, to the



Molecular structures showing the binding of chelated lanthanides and actinides by siderocalin: (a-b) thorium, (c) plutonium, (d) samarium, (e) americium, and (f) curium. The siderocalin is shown in a molecular surface representation, colored by electrostatic potential (red = negative, blue = positive), the chelating group is shown in a licorice-stick representation, colored by atom type (carbon = gray, nitrogen = blue, and oxygen = red), and the metal is shown as a colored sphere.

Rebecca Abergel, Stacey Gauny, Manuel Sturzbecher-Hoehne, and Dahlia An are four of the co-authors of a new paper on the biological chemistry of radioactive metals.

functionalization of targeting biologics for imaging and therapeutic radionuclide delivery, by enabling the selective and stoichiometric chelation of a wide range of elements.



Publication about this research: B.E. Allred, P.B. Rupert, S.S. Gauny, D.D. An, C.Y. Ralston, M. Sturzbecher-Hoehne, R.K. Strong, and R.J. Abergel, “Siderocalin-mediated recognition, sensitization, and cellular uptake of actinides,” *PNAS* **112**, 10342 (2015).

Research conducted by: B.E. Allred, S.S. Gauny, D.D. An, C.Y. Ralston, M. Sturzbecher-Hoehne, and R.J. Abergel (Berkeley Lab) and P.B. Rupert and R.K. Strong (Fred Hutchinson Cancer Research Center).

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