The Grand View League Funded Postdoctoral Fellowship 2018

The American Cancer Society's mission is to save lives, celebrate lives, and lead the fight for a world without cancer.

Nitric oxide (NO) is a reactive signaling molecule that can cause a physiological response by binding to metal ions in proteins. NO is known to react with a cube-shaped cluster of iron and sulfur atoms, commonly referred to as a [4Fe-4S] cluster, in proteins.

DNA repair enzymes are a type of protein that fix sites of damage on DNA to promote healthy cellular function. Some DNA repair enzymes contain [4Fe-4S] clusters. The [4Fe-4S] clusters of DNA repair enzymes were once thought to be of strictly structural significance to help the protein maintain a specific shape. However, it is now known that DNA repair enzymes with [4Fe-4S] clusters can facilitate efficient DNA repair by sending electrons through DNA between other DNA-bound DNA repair enzymes with [4Fe-4S] clusters.

The propensity for NO to react with [4Fe-4S] clusters, together with the importance of [4Fe-4S] clusters in DNA repair, open two currently unanswered questions in the field of DNA repair:

> (1) What is the effect of NO on DNA-bound DNA repair enzymes with [4Fe-4S] clusters?
>
> and (2) What is the effect of NO on signaling between DNA-bound DNA repair enzymes with [4Fe-4S] clusters?

In this proposal, Dr. Ekanger will attempt to address these questions by performing experiments that focus on the study of DNA repair enzymes in the DNA-bound form. Studying the DNA-bound form is critical because the [4Fe-4S] cluster is significantly affected by its proximity to DNA.

He will expand the scope of his studies to human cancer by including a human DNA repair enzyme, MUTYH, which contains a [4Fe-4S] cluster. A mutant of MUTYH was found in a human patient with colon polyps and a family history of colon cancer. The significance of studying the MUTYH mutant is that its [4Fe-4S] cluster is susceptible to degradation, and degradation of the [4Fe-4S] would cause inefficient DNA repair consistent with its association with colon polyps and cancer.

If the MUTYH mutant is more susceptible to degradation by NO, this proposal will discover a new aspect of NO signaling in cancer onset and progression. Ultimately, this proposal will address fundamental questions in NO signaling and DNA repair that are intimately tied to cancer and disease.

The fundamental information gained from this proposal will have implications in the prevention, onset, and treatment of cancerous transformations.

Institution
California Institute of Technology

Investigator
Dr. Levi Ekanger, PhD

Project Title
The Effect of NO on DNA-Bound DNA Repair Enzymes with [4Fe-4S] Clusters

Type of Cancer
Colon and Rectal Cancer

Area of Research
Endogenous Factors in the Origin and Cause of Cancer

Active Through
December 31st, 2021

Total Award Amount
$163,500

American Cancer Society® Attacking from every angle.™

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