Summer Student Research Program
Project Description

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PROJECT TITLE (200 Characters max):
Structure and functional relationship of protein kinase ATM that controls DNA damage response and telomere length

HYPOTHESIS:
The ATM gene codes for a 350 kDa protein kinase consisting of 3056 amino acids. ATM proteins interact with each other and form a homodimer. We will test the hypothesis that protein-protein interaction within the homodimer plays a key role in the catalytic (kinase) activation at DNA damage sites and telomeres.

PROJECT DESCRIPTION **(Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)**
ATM belongs to the superfamily of phosphatidylinositol 3-kinase-related kinases (PIKKs). The PIKK family includes ATR (ATM- and RAD3-related), DNA-PKcs (DNA-dependent protein kinase catalytic subunit) and mTOR (mammalian target of rapamycin). Detailed structures of ATM, ATR, mTOR and DNA-PK are known. Conformation change of ATM during the activation process has not been determined. Although mTOR and DNA-PKcs do not form a homodimer, conformation changes of mTOR and DNA-PKcs during activation have been determined. ATM is encoded by the TEL1 gene in yeast. We will use the UCSF chimera software and generate a computer model of ATM activation using the structural information of mTOR and DNA-PKcs. We will test the model by introducing substitution mutations and carrying out functional genetic studies using yeast cells.
1. We will determine the effect of the ATM mutations on DNA damage repair, checkpoint signaling and telomere homeostasis.
2. We will overexpress and purify ATM mutant proteins, and determine the effect of the mutations on the kinase activity of ATM.

This is part of a collaboration research project between laboratories in Japan and Switzerland.

SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:
https://pubmed.ncbi.nlm.nih.gov/21402778/
https://pubmed.ncbi.nlm.nih.gov/26246601/
https://pubmed.ncbi.nlm.nih.gov/31369547/

THIS PROJECT IS:
Software-based remote work to develop a model and **laboratory work (if allowed)** to test the acquired model

THIS PROJECT IS CANCER-RELATED: Yes
Diseases associated with ATM include Ataxia-Telangiectasia and Mantle Cell Lymphoma.

THIS PROJECT IS HEART, LUNG & BLOOD- RELATED: No
THIS PROJECT INVOLVE RADIOISOTOPES? No
THIS PROJECT INVOLVES THE USE OF ANIMALS No
THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS? No
THIS PROJECT IS SUITABLE FOR:
ALL STUDENTS, who are interested in function and structure relationship

THIS PROJECT IS WORK-STUDY: N/A
THIS PROJECT WILL BE POSTED DURING ACADEMIC YEAR FOR INTERESTED VOLUNTEERS: Yes; can be supported by federal work student program (FWSP).

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

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Students will learn how to use the UCSF Chimera software, a program for the interactive visualization and analysis of molecular structures and will develop skills of how to build up the structure and functional model of relevant proteins. They will further learn how to use Serial Cloner, a software for DNA sequence analysis and test their own model by PCR-based mutagenesis at key amino acid residues or carrying out genetic screening.