



IU BLOOMINGTON

EMERGING AREAS OF RESEARCH

Abstract Template -- Due June 30, 2017

Title of initiative to be proposed:

Building the Future of Structural Biology at Indiana University

Name of lead PI, with title, department/school:

Adam Zlotnick, Professor of Molecular and Cellular Biochemistry/College of Arts and Sciences

Key team member names and departments/schools (up to 10 names):

Suchetana Mukhopadhyay (co-PI, Biology); Carl Bauer (MCB); Steven Bell (MCB/Biology); Yves Brun (Biology); Bogdan Dragnea (Chemistry); Daniel Kearns (Biology); John Patton (Biology); Craig Pikaard (Biology/MCB/HHMI)

Description of area to be proposed. What constitutes this area of research or creative activity as emerging?
(Word limit=500)

Structure is the basis of function at scales from molecular to monumental. Flexibility and heterogeneity have limited our ability to determine structures relevant to biological function. However, the ongoing hardware and software "resolution revolution" in cryo-electron microscopy (cryo-EM) now enables us to reach molecular resolution of virtually any biological material.

Many scientists at IU are heavily invested in the use of cryo-EM for structure determination. Highly funded research on this campus that depends on EM includes the study of viral, bacterial, and eukaryotic ultrastructure, nucleic acid replication/repair machinery, and artificial nanostructures. These researchers have a common need: better structural resolution. To achieve this goal, it is imperative that researchers have state of the art EM equipment on this campus as sample optimization and data collection are iterative processes that are practical and effective only when performed on site.

Enhancing cryo-electron microscopy on this campus will have an immediate impact on IU's world renowned strengths in physical virology and nucleic acid biochemistry. We propose to use EAR funds to purchase a state of the art Talos Arctica electron microscope. Biochemistry will be opening a search for a cryo-microscopist at the Assistant Professor level this year with start up funds supported by the GC Precision Health Initiative. Combining GC and EAR resources will support our strengths and enable us to recruit world class structural biology faculty. Consider two IU-Bloomington examples that highlight our expertise and the need for on-site cryo-EM:

In the Zlotnick lab, structure-function studies of Hepatitis B Virus have led to development of antiviral compounds that dysregulate the viral lifecycle which has directly lead to a high visibility IU-industry partnership. A recent not-yet-published series of cryo-EM structures have shown that these compounds also distort and disrupt intact virus particles, identifying a new mechanism of antiviral action. Our ability to see molecular detail will contribute to the design of new antivirals.

The Pikaard lab uses electron microscopy to study RNA-directed DNA methylation, a process required for genome stability and gene regulation. Misregulation of DNA methylation occurs frequently in human cancers. The pathway is initiated by RNA polymerase IV, a 12-subunit enzyme that converts DNA into a strand of RNA that is then copied by a second enzyme. Preliminary studies have provided an envelope of the complex. To make a huge step forward, the Pikaard lab now needs high-resolution structures to derive function and mechanism. High resolution structures require "ideal" samples and the ability to take thousands of images. The Talos Arctica complements and dramatically expands IU's current electron microscopy infrastructure because Talos has enhanced stability, hardware, and software needed to support automated data collection on multiple samples (autoloading). This upgrade will allow rapidly screening of individual samples necessary to optimize sample conditions to achieve high resolution. Onsite automated cryo-EM will be necessary to competitively recruit outstanding structural biology faculty to this campus. Just a few key hires will make IU -Bloomington a pre-eminent center for the structural biology of supramolecular complexes.

Please submit to earprogram@indiana.edu