

**Application Title: Contributing to the Acquisition of a Titan Cryo-EM**

**Lead Contact for RDF Application:**

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**Key Participating Units: AgriLife, Science, Engineering, Medical School**

**Anticipated Request Amount (\$): \$2,441,808.00**

**Executive Summary:**

Recent advances in cryo-electron microscopy (cryo-EM) hardware and software have profoundly transformed mainstream structural biology, providing access to structures at high resolution with mechanistic details which were thought to be beyond our reach less than a decade ago [1]. The major reason for this transformation is that cryo-EM has distinct advantages over traditional structural biology techniques, like x-ray crystallography and NMR, in that it can be used to elucidate the atomic structures of large, complex, and even flexible macromolecules, many of which cannot be resolved by any other methods. Electron microscopy has long held the promise of structural characterization of macromolecules at atomic resolution. Unfortunately, significant technical barriers resisted progress towards this goal. Over the past two decades there have been significant advances in instrumentation, sample preparation and computational strategies. The initial Nobel Prizes have recently been awarded for these early advances. As was the case for crystallography, many more are anticipated as cryo-EM makes significant contributions to biology going forward. Recently there has been explosive technical progress, which has had many effects. Examples include improvements in direct electron detector camera technology, the methods used to prepare samples, and the development of highly automated data collection and analysis. Finally, the availability of stable 300 kV cryo-EM microscopes have further revolutionized the ability to rapidly solve large macromolecular structures, that were thought to be impossible. Indeed, the best cryo-electron microscopes, like the Titan Krios G4 equipped with a direct detection camera, have been shown to routinely resolve macromolecular complexes to atomic resolution. Such a system provides high-throughput imaging capabilities with robust automated data collection and has become the norm in many successful academic and commercial institutions.

The purchase of a Titan Krios G4 cryo-EM will come from funds committed by AgriLife, and an AgriLife funded CRI request. A pending proposal to CPRIT will cover the remaining costs. We are requesting here that the RDF fund the purchase of a Gatan K3 direct detection camera that is critical to the optimal performance of this instrument, two years of service contract support for the G4 and salary support for a full-time instrumentation specialist to train and assist users in data collection and solving structures.