**MULTI-PI LEADERSHIP PLAN**

This is an interdisciplinary proposal that requires a close collaboration among the investigators and their groups representing three distinct areas: (1) systems biology, (2) biochemistry and molecular biology, and (3) computational biology that are represented respectively by (1) Haiyuan Yu (co-PI), (2) John Lis (co-PI), and (3) Mark Gerstein (co-PI). The participants have complementary expertise, the Yu lab has extensive experience in developing and carrying out high-throughput systems biology experiments and next-generation sequencing techniques. They will develop and optimize MegaMut and CHAIN-seq, generate all WT enhancer clones using Clone-seq, carry out large-scale MegaMut and STROBE-seq experiments, and create CRISPR/Cas9 mutant enhancer knock-in cell lines in Aims 1 and 2. The Lis lab has a strong background in applying biochemistry, molecular and cell biology, and genetics and reverse-genetics approaches to study gene regulation. They will be responsible for developing and optimizing STROBE-seq and detailed *in vivo* study of the effects of mutant enhancers by PRO-seq, ChIP-qPCR, and 4C in Aim 2. The Gerstein lab has considerable expertise in noncoding genome annotation, as part of their 10-year history with the ENCODE and modENCODE projects. They have developed numerous widely-used computational tools, including FunSeq that prioritizes somatic noncoding mutations as potential cancer drivers. They will establish the integrated classifier model, ReEnAct, and work with the Yu lab to implement the innovative three-stage iterative learning framework with real-time experimental parameter optimization in Aim 3.

Dr. Yu, the contact co-PI, will supervise the overall aspects of the project and will be in charge of organizing bi-weekly meetings with all co-PIs, participating postdoctoral fellows, graduate students, and technicians throughout the period of the grant. At these 2 hour meetings, several PowerPoint presentations will be presented by participants who have significant data or technical problems to discuss, and everyone else provides a brief statement on their progress and problems. Drs. Lis and Gerstein will serve as the co-PIs, and work closely with Dr. Yu to provide oversight and take responsibility for the entire project.

The collaborations presented in this proposal are real and vital to the successful completion of our work within the four-year period. Since 2013, Drs. Yu and Lis have been co-advisors for Nate Tippens, a PhD student in the graduate field of Computational Biology and Medicine. The two groups already have graduate students and postdoctoral fellows working productively on various aspects of the proposed project between the two laboratories that generated many of the preliminary results, with regular bi-weekly joint lab meetings. We have been developing a suite of next-generation sequencing, biochemical, chemical, and microscopy tools in very close collaboration. Yu and Lis labs are located at the Cornell University within 5-minutes of walking distance from each other. The close proximity will facilitate regular group meetings and resource sharing. Drs. Yu and Gerstein are both active members of the 1000 Genome Project Functional Interpretation Group (Dr. Gerstein is the co-Chair). Yu and Gerstein labs have been collaborating for several years with many co-publications together, including the most recent 1000 Genome Project papers in ***Nature*** (526: 68–74) and ***Science*** (342: 1235587; Dr. Gerstein is the last and corresponding author and Dr. Yu is one of the senior authors). The two groups have established regular joint lab meetings through conference calls (with PowerPoint files exchanged beforehand) for progress report and problem solving.