June 5, 2017

Dear Mark and Haiyuan,

This letter is to express the full support of the U01 application from the U54 Yale Cancer Systems Biology Center (CaSB@Yale) hosted by Yale Systems Biology Institute. The proposed work will enhance and augment the aims of the Center, particularly through application of the various methods and techniques developed here to the understanding of the etiology, progression and control of prostate cancer. We will be happy to make these techniques available through the Center Cores and other facilities and through collaborative work. As the Director of the Center and the Institute, I am very happy to support this application with the highest degree of enthusiasm, and to commit my own time and the resources of my lab in particular to the proposed project.

CaSB@Yale is dedicated to the analysis of phenotypic switching in cancer cells, promoting initiation of invasive spread from the primary tumor. The current focus of the Center is on the particularly aggressive cancer types, prone to quick and effective dissemination accompanied by both proliferative and migratory cellular phenotypes. To investigate how cells within a tumor population display the co-existence of the ‘go or grow’ phenotypes, the Center is employing an array of novel techniques, ranging from synthetic biology to evolutionary theory. In particular, we have developed a range of new platforms and methods taking advantage of advanced CRISPR-Cas based genome editing and using micro- and nano-fabrication to mimic the complex in vivo micro-environments and sort out cells displaying diverse phenotypic characteristics. These latter techniques, developed within the Center cores will be particularly useful for the research proposed in this U01 application.

In specific terms, the proposed work will benefit from the resources available through Core 1 (microfabrication core that will supply the experimental platforms for the RACE assay described in the text) and Core 2 (animal/CRISPR core) that will assist with the generation of the components of the CRISPR libraries for transfection of the RWPE-1 - prostate normal cell line and PC3 prostate cancer cell line. This work will be particularly synergistic with the aims of the Center.

The Yale Systems Biology Institute is a highly interactive and multidisciplinary research unit, with 9 research labs from 3 different schools and 7 different departments, jointly working on a project that is supported by the new Cancer Systems Biology Grant. The diverse focus areas represented by the institute members range from synthetic biology to evolutionary theory. Overall, the researchers at the institute and the center are committed to investigation of the complex interactions in biological systems, on multiple levels, ranging from the analysis of biological fundamentals to practical application and development of new methods and techniques. Furthermore, the Center is a part of the NCI-sponsored multi-institutional consortium and has formed close communication and collaborations with multiple departments and centers at Yale and beyond, including Yale Cancer Center, Yale Cancer Institute, Yale Networks Institute, in areas ranging from basic biology to clinical applications. The Institute and the center are housed on two floors of a research building next door to 5 other similarly interdisciplinary institutes. It is located on the West Campus of Yale University providing further core facilities, including the Center for Genome Analysis, Imaging Center and new Microfabrication Facility. All these resources and expertise will be available to the researchers on the current U01 application, which will create wonderful synergies and will be mutually beneficial.

Let me again express my post enthusiastic support for this application. It will result in important insights into etiology, progression and control of prostate cancer.

Yours truly,

Andre



Andre Levchenko

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