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CHRB Grant Title: ***BRCA1-directed Transcriptional Regulation in Hereditary Breast Cancer***

CHRB Project Summary:

Today, women diagnosed with breast cancer have a higher chance of survival than ever before—especially when it's detected early. However, triple negative breast cancer threatens the lives of many young women in Virginia. This form of breast cancer is extremely aggressive, is more likely to recur, and it presents major challenges for treatment. Treatment options are limited, and there is currently no known cure. We will investigate the actions of a prime culprit implicated in causing the disease, the protein factor, BRCA1. We will determine, in 3D, how BRCA1 interacts with other complex proteins poised on DNA to induce cancer. The 3D model elucidates unique protein-DNA properties and will greatly contribute to the design of new drugs that interfere with cancer-causing processes. We expect this will lead to new treatment options aimed at combating triple negative breast cancer and enhancing clinical outcomes.

CHRB Project Outcome:

Breast cancer is the most common cancer among women in the United States, with the highest mortality rates among women in the Mid-Atlantic region. In Virginia, geographical and racial disparities regarding clinical outcomes still persist. Upon considering incidence, local staging, mortality, and screening prevalence, the Virginia Department of Health has identified Richmond City, Rappahannock/Rapidan, Portsmouth, Chesterfield, and Cumberland Plateau districts at high risk for triple negative breast cancer incidences. By identifying new molecular targets for drug design aimed at this aggressive form of breast cancer, we strive to reduce cancer-related mortality for women living in Virginia. Working toward this goal, we have produced a streamlined system to isolate and evaluate the molecular structure and operations of BRCA1 in the context of patient-derived human breast cancer cells with and without genetic mutations. Results from this work bring us a step closer to resolving the impact of BRCA1 mutations in triple negative breast cancer patients in Virginia and beyond.

Comments regarding CHRB Grant Funding

The CHRB grant funding helped spark our breast cancer initiatives by providing instrumental resources and financial support. This support led to high quality publications in peer-reviewed academic journals. Our continued productivity paved the way for establishing a track record of external funding from the National Institutes of Health and the National Cancer Institute. Our team is very grateful for the opportunity to represent the CHRB and promote its mission to support investigators on local and national fronts.

Leveraged Funding as a result of CHRB Grant Award: $6,055,000

Awarded:

Project title: ***Molecular Basis for BRCA1 in Transcription-Coupled Repair Mechanisms***
Funding agency: Concern Foundation – Young Investigator award
Awarded: July 2014
Amount awarded: $120,000

Project title: ***Tunable Microchip Sorting of BRCA1 Nuclear Assemblies***
Funding agency: NIH / NCI – R01
Awarded: July 2015
Amount awarded: $1,800,000

Project title*: Decoding the Role of BRCA1 in Brain Cells using High-Resolution Cryo-EM*
Funding agency: UVA-VTC Seed Grant
Awarded: January 2016
Amount awarded: $75,000

Project title*: Hot Spot Analysis of the Breast Cancer Susceptibility Protein*
Funding agency: NIH / NCI – R01
Awarded: March 2018
Amount awarded: $1,960,000

Project title: ***Multi-scale Imaging of Breast Cancer Proteins during DNA Repair***
Funding agency: NIH / NCI – R01
Awarded: June 2018
Amount awarded: $2,100,000

Publications (*indicates Kelly as corresponding author)

Gilmore BL, Varano AC, Dearnaley W, Liang Y, Marcinkowski BC, Dukes MJ, **Kelly DF*** (2018) Preparation of Tunable Microchips to Visualize Native Protein Complexes for Single Particle Electron Microscopy. *Protein Complex Assembly: Methods and Protocols (in press).*

Liang Y, Dearnaley W, Varano AC, Winton CE, Gilmore BL, Alden NA, Sheng Z, and **Kelly DF*** (2017) Structural Analysis of BRCA1 Reveals Modification Hot Spot. *Science Advances.* (*3*) e1701386.

Gilmore BL, Liang Y, Winton CE, Patel K, Karageorge V, Varano AC, Dearnaley W, Sheng Z, and **Kelly DF*** (2017) Molecular Analysis of BRCA1 in Human Breast Cancer Cells Under Oxidative Stress. *Sci. Rep.* (*7*) 43435.

DiMemmo L, Varano AC, Haulenbeek J, Liang Y, Patel K, Dukes MJ, Zheng S, Hubert M, Piccoli S, and **Kelly DF*** (2017) Real-time observation of protein aggregates in pharmaceutical formulations using liquid cell electron microscopy. *Lab on a Chip* (*17*) 315-322.

Winton CE, Gilmore BL, Tanner JR, Dukes MJ, Sheng Z, and **Kelly DF*** (2017) Tunable substrates improve imaging of viruses and cancer proteins. *Microscopy Today* 25(04) 22-27.

Demmert AC, Dukes MJ, Pohlmann E, Patel K, Varano AC, Sheng Z, McDonald SM, Spillman M, Mirsaidov U, Matsudaira P, and **Kelly DF*** (2016) Visualizing Macromolecules in Liquid at the Nanoscale. (Chapter 17) *Liquid Cell Electron Microscopy*. Frances Ross (editor), Cambridge University Press.

Winton CE, Gilmore BL, Demmert AC, Karageorge V, Sheng Z, **Kelly DF*** (2016) A microchip platform for structural oncology applications. *npj Breast Cancer 2,* 16016.

Delatch DL, Dukes MJ, Varano AC, **Kelly DF**, Dukes AD (2015) Real-time imaging of lead nanoparticles in solution – determination of the growth mechanism. *RSC Advances* 5:104193.

Varano AC, Rahimi A, Dukes MJ, Poelzing S, McDonald SM, and **Kelly DF*** (2015) Visualizing Virus Particle Mobility in Liquid at the Nanoscale. *Chem. Comm.* (51), 16176-16179.

Gilmore BL, Winton CE, Demmert AC, Tanner, JR, Bowman S, Karageorge V, Patel K, Sheng Z, and **Kelly DF*** (2015) A Molecular Toolkit to Visualize Native Protein Assemblies in the Context of Human Disease. *Sci. Rep.* 5:14440.

Rahimi A, Varano AC, Demmert AC, Melanson LA, McDonald SM, and **Kelly DF*** (2015) A Non-Symmetric Reconstruction Technique for Transcriptionally-Active Viral Assemblies. *J. Anal. Mol. Tech.* 2(1) 1-6.

Pohlmann ES, Patel K, Guo S, Dukes MJ, Sheng Z, and **Kelly DF*** (2015) Real-time Visualization of Nanoparticles Interacting with Glioblastoma Stem Cells. *Nano Letters* 15(4) 2329-2335.