Grant establishes center for 3-D structure and physics of the genome at UMMS

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The University of Massachusetts Medical School has been awarded a five-year, $15 million grant from the National Institutes of Medicine Common Fund to establish the Center for 3-D Structure and Physics of the Genome. The center is part of the NIH's 4-D Nucleome Program, an interdisciplinary effort comprising 29 research teams across the country with the goal of mapping the three-dimensional architecture of the human genome and how this organization changes over time—the fourth dimension. The goal is to understand how 3-D genome structure influences gene expression, cellular function, development and disease. In total, UMMS received three grants for as much as $18.7 million as part the multiyear effort.

"We've entered what can be considered the third phase of the human genome project," said Job Dekker, PhD, Howard Hughes Medical Institute Investigator, professor of biochemistry & molecular pharmacology and co-director of the Program in Systems Biology. "The first two phases were focused on decoding the genome's sequence and annotating it. With this new phase we want to understand how the various genes and regulatory elements that make up the genome talk to each other and collaborate together in real-time to influence biology and disease."

Although DNA is composed of a linear sequence of bases, it doesn't exist inside the cell nucleus in a simple, straight form. More like a ball of cooked spaghetti, the genome folds and loops back on itself so it can fit inside the tight confines of the nucleus. The shape it takes has a

profound influence on which genes in a cell are turned on or turned off. And this 3-D architecture varies from cell type to cell type and even between cell states. To properly understand how the genome works to coordinate gene expression, it's necessary to understand how and why the genome is organized in space.

Dr. Dekker is a pioneer in the study of the three-dimensional structure of the genome. He developed the chromosome conformation capture technologies, biochemical techniques for determining how DNA segments interact and are linked to one another, which are the heart of the '3C,' '5C,' 'Hi-C' and 'Micro-C' tools used by researchers worldwide to map the structure and organization of chromosomes inside cells.

"Professor Dekker's work is at the cutting edge of connecting the structure of DNA with its function, one of the final frontiers in understanding gene regulation," said Terence R. Flotte, MD, the Celia and Isaac Haidak Professor of Medical Education, executive deputy chancellor, provost and dean of the School of Medicine.

Using chromosome conformation capture technologies in conjunction with advanced computational modeling and a range of imaging methods, the center will generate three dimensional models of the human genome inside fibroblast cells during metaphase and interphase, as well as in embryonic stem cells in undifferentiated and differentiated states. From these, Dekker and colleagues hope to uncover similarities between the genomic structures that point to general rules that govern how and why genomes fold in all cells.

Once they've generated these 3-D genomic models, Dekker's team will use gene editing techniques to biologically validate genetic functions linked to structure. With tools such as CRISPR/CAS9, researchers at the center will be able to label specific parts of the genome so that they can be visualized in the microscope, and they will be able to make changes to

the DNA sequence so that the 3-D folding can be perturbed in a highly targeted manner.

"We will genetically engineer the genome to surgically perturb or alter the way it is folded. We will then determine how this influenced how genes are regulated," said Dekker. "With this we'll begin to understand which aspects of the 3-D structure of the genome control gene function."

Finally, the center will develop entirely new technologies for locally mapping the spatial organization of the genome. These technologies, unlike the chromosome conformation capture technologies that map interactions genome-wide, will allow scientists to zoom in on small, defined regions of the genome and to identify the proteins and other molecules that bind to the genome to facilitate local folding.

Provided by University of Massachusetts Medical School