Genome engineering to improve public health.

Synopsis:
Almost every disease has a genetic component. Often this information is used only to determine how doomed a person is to develop disease. We would like to use the genetic information to fix the disease. A guiding principle for our work has been to study how nature does what it does, then attempt to use that knowledge to make useful tools to improve public health, either through increased knowledge or therapeutic intervention. Specific research foci in the Segal Lab revolve around engineering zinc finger, TALE, and CRISPR nucleases and transcription factors.

Designing permanent inactivators of HIV. We are designing CRISPR nucleases to chop up the integrated DNA form of the HIV provirus without affecting any human sequences. Unlike most other anti-HIV therapies, this approach would permanently inactivate the virus. It should also be useful in patients with viruses that use CXCR4, for whom CCR5 entry inhibitors would be ineffective (i.e., most infected patients). We are also developing novel delivery methods.

Manipulating epigenetic mechanisms in Angelman, Prader-Willi, and Dup15q Syndromes. These are rare neurogenetic diseases that cause autism-spectrum symptoms, but their genetics has made them the textbook examples of imprinting disorders. We are using zinc finger-based artificial transcription factors to activate the epigenetically silenced genes in these diseases.

Manipulating genetic variation in Coronary Artery Disease (CAD). Several genetic variations (SNPs) have been recently associated with an increased risk of CAD. We are using CRISPR nucleases to engineer defined haplotypes into human induced pluripotent stem cells (hiPSC) in order to understand the functional role of these variants. Our approach overcomes the historic barrier of trying to study the affects of specific human mutations in a background of millions of other genetic differences between two individuals.

Using our genomes to improve public health. Directly, or through collaboration, our research interests span colorectal cancer, breast cancer, neurofibromatosis, Down syndrome, Rett Syndrome, and stem cell reprogramming. We are applying our technology to make improved preclinical animal models of disease, drawing on the strategic strengths of UC Davis in human medicine, veterinary medicine, animal science, and genome science.

High-throughput investigations of CRISPR-DNA interactions. We continue to develop new methodologies for genome editing, such as methods to study off-target activity of CRISPRs and factors for targeted epigenetic modification. We employ methods of directed evolution for protein engineering and ChIP-seq and RNA-seq to examine the effects of tools on a genome-wide scale.
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