



## David R. Liu

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David R. Liu is the Richard Merkin Professor, Director of the Merkin Institute of Transformative Technologies in Healthcare, and Vice-Chair of the Faculty at the Broad Institute of Harvard and MIT; Thomas Dudley Cabot Professor of the Natural Sciences and Professor of Chemistry and Chemical Biology at Harvard University; and Howard Hughes Medical Institute Investigator. Liu graduated first in his class at Harvard in 1994. He performed organic and bioorganic chemistry research on sterol biosynthesis under Professor E. J. Corey's guidance as an undergraduate. During his Ph.D. research with Professor Peter Schultz at U. C. Berkeley, Liu initiated the first general effort to expand the genetic code in living cells. He earned his Ph.D. in 1999 and became Assistant Professor of Chemistry and Chemical Biology at Harvard University in the same year. He was promoted to Associate Professor in 2003 and to Full Professor in 2005. Liu became a Howard Hughes Medical Institute Investigator in 2005 and joined the JASONS, academic science advisors to the U.S. government, in 2009. Liu has earned several university-wide distinctions for teaching at Harvard, including the Joseph R. Levenson Memorial Teaching Prize, the Roslyn Abramson Award, and a Harvard College Professorship. Liu has published >175 papers and is the inventor of >65 issued U.S. patents. His research accomplishments have earned distinctions including the Ronald Breslow Award for Biomimetic Chemistry, the American Chemical Society Pure Chemistry Award, the Arthur C. Cope Young Scholar Award, and awards from the Sloan Foundation, Beckman Foundation, NSF CAREER Program, and Searle Scholars Program. In 2016 he was named one of the Top 20 Translational Researchers in the world by *Nature Biotechnology*, and in 2017 was named to the *Nature's* 10 researchers in world and to the *Foreign Policy* Leading Global Thinkers. Professor Liu's research integrates chemistry and evolution to illuminate biology and enable next-generation therapeutics. His major research interests include the engineering, evolution, and *in vivo* delivery of genome editing proteins such as base editors to study and treat genetic diseases; the evolution of proteins with novel therapeutic potential using phage-assisted continuous evolution (PACE); and the discovery of bioactive synthetic small molecules and synthetic polymers using DNA-templated organic synthesis and DNA-encoded libraries. Base editing (named one of four 2017 Breakthrough of the Year finalists by *Science*), PACE, and DNA-templated synthesis are three examples of technologies pioneered in his laboratory. He is the scientific founder or co-founder of six biotechnology and therapeutics companies, including Editas Medicine, Pairwise Plants, Exo Therapeutics, and Beam Therapeutics.

### **Abstract: Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells**

Point mutations represent most known pathogenic human genetic variants but are difficult to correct cleanly and efficiently using standard nuclease-based genome editing methods. For most point mutations that cause genetic disease, simply cutting the mutated gene is not expected to offer therapeutic benefit, because the function of the mutated gene needs to be restored, not further disrupted. In this lecture I will describe the development, application, and evolution of base editing, a new approach to genome editing that directly converts a target base pair to another base pair in living cells without requiring double-stranded DNA breaks or donor DNA templates. Through a combination of protein engineering and protein evolution, we recently developed two classes of base editors (CBE and ABE) that together enable all four types of transition mutations (C to T, T to C, A to G, and G to A) to be efficiently and cleanly installed or corrected at target positions in genomic DNA. The four transition mutations collectively account

for most known human pathogenic point mutations. Base editing has been widely used by many laboratories around the world in a wide range of organisms including bacteria, fungi, plants, fish, mammals, and even human embryos. We have recently expanded the scope of base editing by enhancing its efficiency, product purity, targeting scope, DNA specificity and *in vivo* delivery. By optimizing base editor expression, we developed “max” versions of cytosine and adenine base editors with greatly increase editing efficiency in mammalian cells. We also show that base editing can function *in vivo* in post-mitotic somatic cells that do not support homology-directed repair. To improve the targeting scope of base editing, we used our phage-assisted continuous evolution (PACE) system to rapidly evolve both Cas9 and base editor variants with broadened PAM compatibility, higher DNA specificity, and enhanced editing capabilities. Finally, we integrated several of these developments, including efficient *in vivo* delivery of CBEs and ABEs, to address cell and animal models of human genetic disease. Base editing can be used to correct pathogenic point mutations, introduce disease-suppressing mutations, and create new models of genetic diseases.

### Five Key References

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