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Wendell Lim is the Byers Distinguished Professor of the Department of Cellular and Molecular Pharmacology at the University of California San Francisco, and the Director of the UCSF Cell Design Institute and the UCSF NCI Center for Synthetic Immunology. He received his A.B. in Chemistry, *summa cum laude,* from Harvard College, his Ph.D. in Biochemistry and Biophysics at the Massachusetts Institute of Technology and completed his postdoctoral training at Yale University. His research focuses on the design principles of molecular circuits that govern cell decision-making and responses. His lab has made contributions in understanding the molecular machinery of cell signaling and how molecular modules have been used in evolution to build novel behaviors. More recently he has been a pioneer in the emerging field of synthetic biology, exploring how these design principles can be harnessed to engineer living cells with precision therapeutic response programs against diseases such as cancer, autoimmunity, neuroinflammation, and degeneration. He was founder of one of the first synthetic biology cell therapy companies, Cell Design Labs, and is author of the textbook, *Cell Signaling: Principles and Mechanisms*.

Abstract: "Re-Thinking Cancer Targeting in the Era of Smart Cell Therapeutics"

In the past few decades, cancer therapeutics have increasingly focused on precision targeting of single cancer-associated molecules. Despite great advances, such targeted therapies still show incomplete precision and the eventual development of resistance due to target heterogeneity or mutation. However, the recent development of cell-based therapies such as chimeric antigen receptor (CAR) T cells presents a revolutionary opportunity to reframe strategies for targeting cancers. Immune cells equipped with synthetic circuits are essentially living computers that can be programmed to recognize tumors based on multiple signals, including both tumor cell-intrinsic and microenvironmental features. Moreover, cells can be programmed to launch broad but highly localized therapeutic responses that can limit the potential for escape while still maintaining high precision. For example, we have developed novel multi-step "prime-then-kill" synthetic Notch-->CAR multi-receptor circuits that increase the precision of tumor killing by requiring the sequential recognizing two or more antigens. Recently we have used these multi-receptor circuits to integrate tumor recognition information from different scales. For example, we have designed synthetic Notch receptors that recognize unique natural features of specific tissues, such as the brain or the lung. We can then use these receptors to induce the expression of CAR's that recognize a tumor surface antigen, selectively in the target organ (e.g. the brain). These circuits thus integrate an anatomical (and non-disease) recognition with tumor specific antigen recognition, leading to much higher targeting specificity. We have used this kind of anatomical recognition to design more precise and effective brain tumor cell therapies, as well as cell therapies directed against a broader set of neurological disorders such as neuroinflammation and neurodegeneration. This type of complex multi-scale recognition is simply impossible to achieve with standard molecular therapeutics, but can be uniquely achieved with an engineered living cell therapeutic. Using these types of circuits, genomic/proteomic tumor data could in principle be used with artificial intelligence to guide how to most effectively design circuits for each disease. We have initiated clinical trials for glioblastoma and pancreatic cancer that harness these types of next generation recognition circuits.