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	Undergraduate degree, University of York, York, UK
	M.A. and Ph.D., Harvard University, Cambridge, MA
1978	Assistant Professor, Stanford University, Stanford, CA
1991	Professor, Department of Molecular Pharmacology, Stanford University
1997	Director, Gene Therapy Technology and Chair, Department of Molecular Pharmacology, Stanford University

Honors

1995	Membership in the Institute of Medicine of the National Academy of Sciences
1996	Fellow of the American Academy of Arts and Sciences
1999	Excellence in Science Award, Federation of American Societies for Experimental Biology
present	Board of Directors, American Society of Gene Therapy
present	Council of the National Institute of Aging

Regulating the Regulators

In eukaryotes, chromatin-embedded genes are inactive in their basal state. Nevertheless, many genes involved in controlling cell growth and developmental processes are actively repressed. Their activation is controlled by extracellular signals that trigger the release of transcriptional repressors and promote the binding of activators, often to the same promoter element. Transcription factor networks that follow this model include Myc, E2F, and nuclear hormone receptors among others. To study the mechanism underlying this phenomenon, we have created a tetracycline (tet) regulable synthetic system that allows the expression of activators and repressors together (Retrotet ART) due to the introduction domains that prevent non-functional heterodimers from forming. Using retroviral vectors, the system can be rapidly and efficiently delivered to populations of cells. Moreover, this system has an extraordinary dynamic range, from a barely detectable level of expression to up to 6 orders of magnitude above that level[1]. This system has allowed us to monitor the effect of different amounts of bound activator or repressor on transcription from individual promoter-reporter cassettes. We have found that increased binding of a transcriptional activator alone results in a dose-dependent increase in transcription from each single promoter. Decreasing binding of a transcriptional repressor is converted to a threshold response and no intermediate levels of gene expression are observed. This finding fits well with the notion that growth and differentiation are generally all-or-none responses. Our results suggest that a repressor-activator interplay functions to establish a switch that facilitates all-or-none responses to extracellular signals.

1. Rossi et al. *Nature Genetics* (1998).