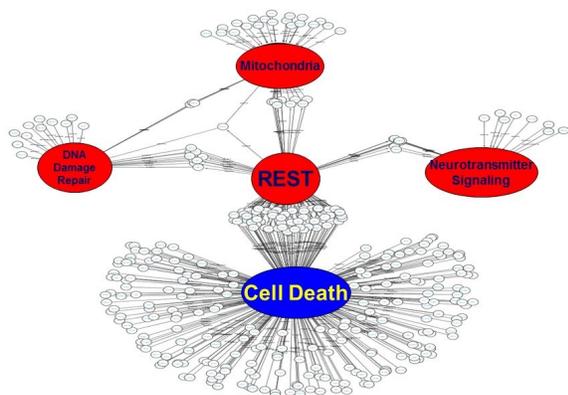# Department of Biochemistry

2017 Axelrod Distinguished Lectures

Bruce Yankner

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Professor of Genetics and Neurology, Harvard Medical School

Monday, April 3
3:30 - Deans Auditorium (PFEN 241)
REST and Stress Resistance in Aging and
Alzheimer's Disease

Tuesday, April 4
1:30 - Deans Auditorium (PFEN 241)
Transcriptional Regulation of Lifespan

REST and Stress Resistance in Aging and Alzheimer's Disease: Our studies of aging began when we defined the first gene expression signature of the aging human brain. Subsequent advances in bioinformatics enabled us to use the gene expression signature of aging to predict relevant transcriptional regulators. This led to a surprising result: The transcriptional repressor REST, which had previously been implicated in brain development, and other components of this corepressor pathway, were predicted to be among the most central regulators of the aging brain transcriptome. This prediction was confirmed biochemically. We found that REST/NRSF is induced in the aging human brain and coordinates the expression of a gene network that protects aging neurons from neurotoxic stress, synapse loss and overexcitation. It performs these functions by regulating the expression of genes that are involved in cell death, inflammation, oxidative stress and the pathology of Alzheimer's disease. The induction of REST correlates with preservation of cognitive function during aging, whereas loss of REST is associated with cognitive decline. I will discuss studies that provide insights into the regulatory role of the REST network in protecting aging neurons using REST conditional knockout mice and cell culture models. Transcriptome sequencing and ChIP-seq analysis have been used to define the REST-regulated gene network. By applying a systems genetics approach to well-characterized human brain samples from large aging cohort studies, we are defining REST-regulated gene networks predictive of successful aging, early cognitive decline and Alzheimer's disease. A central question is how this gene network systematically fails in individuals who develop Alzheimer's disease, and whether this decline can be reversed. The biology of the REST pathway raises the exciting possibility that the aging brain could be protected by a novel therapeutic approach based on activation of the brain's own defense network.

Transcriptional Regulation of Lifespan: Cognitive frailty is emerging as one of the great health threats of the twenty first century. As the life expectancy of the population has increased, so too has the prevalence of cognitive decline and dementia, largely in the form of Alzheimer's disease, which now afflicts almost 50% of adults over the age of 85. This startling figure can only grow as the average age of the population rises, so understanding the basis of cognitive decline during aging is critical. The greatest risk factor is age itself. So the development of this pathology must be understood in the context of the molecular biology of the aging process. A major clue is that Alzheimer's disease only occurs in aging humans, although aspects of its pathology can be observed in other mammals, particularly non-human primates. The question I will pose is whether evolutionary changes in the human brain, while providing enormous selective advantages during the reproductive years, also play a role in cognitive decline and dementia during post-reproductive aging. I will also discuss new findings suggesting that transcriptional mechanisms which regulate neural aging also regulate lifespan at an organismal level.

About the Axelrod Lectures:

D r. Bernard Axelrod served as Head of the Department of Biochemistry. His efforts were instrumental in founding the biochemistry program at Purdue University. On the occasion of his 70th birthday, colleagues and friends established this lectureship in honor of Dr. Axelrod's many contributions to the field of biochemistry and its community of scientists. Dr. Axelrod passed away in 2011 at the age of 97.