C. David Allis, Ph.D.

TRI-INSTITUTIONAL PROFESSOR • JOY AND JACK FISHMAN PROFESSOR, LABORATORY OF CHROMATIN BIOLOGY AND EPIGENETICS

All the cells in the human body have the same genes, but only a small percentage of genes are active in any given cell at any given time. Allis studies chromatin, the DNA–histone protein complex that packages the genetic information within each cell. Chromatin can facilitate or restrict access to specific genes, and serves as a means of gene regulation that lies outside of the DNA itself—the basis of a field known as epigenetics.

Chromatin is the physiological template of the human genome. Nature has evolved sophisticated mechanisms to alter it and thereby regulate gene expression and other biological processes.

One such mechanism involves the addition or loss of chemical groups. The Allis lab is investigating how covalent histone modifications regulate biological processes in a variety of unicellular and multicellular eukaryotic models. Through enzymatic processes such as acetylation, methylation, phosphorylation, and ubiquitylation, histones are believed to function like master on-off switches that determine whether particular genes are active or inactive. Disease links, notably cancer, are often linked to alterations in epigenetic regulators, and insights into the mechanisms that turn particular genes on or off could lead to better treatments.

Because histone proteins are often subject to frequent, high-density posttranslational modifications (PTMs), the Allis lab hypothesizes that PTMs are found in strategic locations along the histone tail, allowing the cell to reversibly deal with gene silencing or activation. The lab has been a front-runner in deciphering elaborate crosstalk relationships within the same histone tails (cis) or across distinct histone tails (trans). These combinatorial changes appear to govern chromatin function in a variety of processes, and have been termed the "histone or epigenetic code," a widely cited and influential hypothesis.

The Allis lab has also investigated mutations in histone H3 that are highly enriched in pediatric gliomas (including the substitution of H3 lysine 27 for methionine, or H3K27M). The team has shown that these so-called oncohistone mutations can alter the recruitment and activity of histone-modifying complexes, and therefore change the epigenetic landscape and gene expression. Given the restricted distribution of these mutations to pediatric gliomas, the Allis lab further hypothesizes that a cell-lineage specific cellular context is crucial for the ability of these mutations to mediate oncogenesis. In support of this idea, current findings have documented that the substitution of H3 lysine 36 for methionine (H3K36M) impairs the differentiation of mesenchymal progenitor cells and generates a type of tumor called undifferentiated sarcoma in vivo. H3K36M mutations have also been documented in a subset of head and neck squamous cell carcinomas. Studies in the lab are now expanding the landscape of oncohistones to a wide range of diverse tumor types and developmental syndromes.

Another area of focus for the lab involves so-called reader proteins that interpret histone modifications. The team discovered that the protein ENL, a reader of histone acetylation, activates oncogenic gene expression programs in human leukemia. They also showed that recurrent mutations in the YEATS domain of ENL drive the formation of Wilms' tumor, the most common pediatric kidney cancer. These data suggest that displacing ENL from chromatin may be a promising therapy. Active investigations are underway to test this hypothesis with collaborators in clinically relevant settings, including human patients.

EDUCATION

B.S. in biology, 1973
University of Cincinnati

M.S. in biology, 1975
Ph.D. in biology, 1978
Indiana University

POSTDOC

University of Rochester, 1978–1981

POSITIONS

Assistant Professor, 1981–1986
Associate Professor, 1986–1989
Professor, 1989–1990
Baylor College of Medicine

Professor, 1990–1995
Syracuse University

Professor, 1995–1998
University of Rochester

Professor, 1998–2003
University of Virginia Health System

Professor, 2003–
The Rockefeller University

AWARDS

Dickson Prize, 2002

Massry Prize, 2003

Wiley Prize, 2004

Canada Gairdner International Award, 2007

ASBMB-Merck Award, 2008

Lewis S. Rosenstiel Award, 2011

Japan Prize, 2014

Charles Leopold-Mayer Prize, 2014

Breakthrough Prize, 2015

Gruber Genetics Prize, 2016

March of Dimes Prize, 2017

Ernst W. Bertner Memorial Award, 2018

Albert Lasker Basic Medical Research Award, 2018

Hope Funds for Cancer Research Award in Basic Science, 2021

Elaine Redding Brinster Prize in Science or Medicine, 2022

Albany Medical Center Prize, 2022

HONORARY SOCIETIES

National Academy of Sciences

National Academy of Medicine

American Academy of Arts and Sciences

French Academy of Sciences

SELECTED PUBLICATIONS

Wan, L. et al. Impaired cell fate through gain-of-function mutations in a chromatin reader. *Nature* 577, 121–126 (2020).

Weinberg, D.N. et al. The histone mark H3K36me2 recruits DNMT3A and shapes the intergenic DNA methylation landscape. *Nature* 573, 281–286 (2019).

Nacev, B.A. et al. The expanding landscape of 'oncohistone' mutations in human cancers. *Nature* 567, 473–478 (2019).

Wan, L. et al. ENL links histone acetylation to oncogenic gene expression in acute myeloid leukaemia. *Nature* 543, 265–269 (2017).

Lu, C. et al. Histone H3K36 mutations promote sarcomagenesis through altered histone methylation landscape. *Science* 352, 844–849 (2016).