BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Armache, Karim-Jean

eRA COMMONS USER NAME (credential, e.g., agency login): karmache

POSITION TITLE: Assistant Professor of Biochemistry and Molecular Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Technical University of Lodz	M.S.	2000	Biochemistry
Ludwig Maximilian University of Munich	Ph.D.	2005	Biochemistry
Ludwig Maximilian University of Munich	Postdoc	2005-06	Biochemistry
Massachusetts General Hospital	Postdoc	2006-13	Biochemistry and Molecular Biology

A. Personal Statement

Despite advances in the molecular understanding how chromatin regulates transcription, there is limited knowledge of this process at a mechanistic level. The goal of my laboratory is to understand the organization and dynamics of silent chromatin. We use a combination of structural approaches, including X-Ray crystallography and cryo electron microscopy (cryoEM) , coupled with biophysical and biochemical experimentation to study mechanisms by which macromolecular complexes change DNA accessibility to regulate transcription. Gene silencing factors such as Polycomb Repressive Complexes (PRC), the Silent Information Regulator (SIR) complex or Heterochromatin Protein 1 (HP1) specifically bind and organize nucleosomes to form higher-order, compacted chromatin structure. Posttranslational modifications of histones are known to regulate binding of these factors. Molecular details of these complexes will be pivotal to understanding their biological function in both normal and disease states and will be central to the development of novel epigenetics based therapeutics.

B. Positions and Honors

Positions and Employment

2005 -2006 Postdoctoral Fellow at Gene Center, Ludwig Maximilian University, Munich, Germany
2006 -2013 Postdoctoral Fellow, Department of Genetics, Harvard Medical School, Boston, MA, Massachusetts General Hospital, Boston, MA
2013 Assistant Professor, Skirball Institute of Biomolecular Medicine, NYU Medical School, New York, NY

Honors

2007 - 2010 Human Frontiers Science Program Long-Term Fellowship
2014 Kimmel Scholar
2015 Packard Fellow

C. Contributions to Science

Mechanisms of gene transcription by RNA polymerase II

RNA polymerase II (Pol II) is a central enzyme responsible for transcription of all protein coding genes. My work revealed the structure of a complete 12-subunit Pol II in its initiation competent form. We also determined other important higher-order Pol II structures that shed light on mechanisms of transcription initiation (with the general transcription initiation factor TFIIB) and elongation and proofreading (with nucleic acids and TFIIS). Structural work was complemented with biochemistry and genetics to rationalize the transitions between transcription initiation and elongation and to unravel similarities and differences between eukaryotic and prokaryotic transcription machineries.

Armache KJ, Kettenberger H, Cramer P. (2003). Architecture of initiation-competent 12-subunit RNA polymerase II. Proc. Natl. Acad. Sci. U.S.A. National Acad Sciences, 100(12), 6964–8. PMCID: PMC165813

Kettenberger* H, **Armache* KJ**, Cramer P. (2004). Complete RNA polymerase II elongation complex structure and its interactions with NTP and TFIIS. Molecular Cell, 16(6), 955–65. *Equal contribution

Kostrewa* D, Zeller* ME, **Armache* KJ**, Seizl M, Leike K, Thomm M, et al. (2009). RNA polymerase II-TFIIB structure and mechanism of transcription initiation. Nature, 462(7271), 323–30. *Equal contribution

Mechanisms of gene silencing in eukaryotes

Gene silencing is a fundamental process essential for development of all eukaryotes. Specific proteins and protein complexes bind and modify nucleosomes to repress transcription. Deregulation of gene silencing can lead to many developmental diseases including cancer. Even though these processes have been studied using genetics, molecular biology and other techniques the atomic details of gene silencing proteins and especially their complexes with nucleosomes are still enigmatic. During my postdoctoral work at MGH I focused on the yeast SIR complex as a model for gene silencing in all eukaryotes. During that time I determined a 3.0Å crystal structure of the functional domain of Sir3 (essential protein in the SIR complex) with a nucleosome core particle. This work provided the first atomic visualization of a structure that silences genes, and just the second crystal structure of any protein in complex with a nucleosome. Silencing of the yeast mating type loci by Sir3 has been a paradigm in the field of epigenetic silencing, with over 40 years of work defining the proteins involved and the nature of the silenced domain that maintains cell fate in yeast. Our structure explained at an atomic level over 30 genetic interactions, including how the H4 N-terminal tail interacts with Sir3 and how covalent modification of Lysine 16 of the tail and lysine 79 in the body of histone H3 regulate binding by Sir3. The paper thus provided novel advances in determining how proteins interact with nucleosomes, in describing how an epigenetically stable silenced chromatin structure forms, and in explaining at the atomic level how covalent modifications of histones regulate this process. This paper is a landmark study in epigenetic regulation and it provides the first visualization of a structure that silences genes important to determining cell fate, a hallmark issue in epigenetics

Armache KJ, Garlick JD, Canzio D, Narlikar GJ, Kingston RE. (2011). Structural basis of silencing: Sir3 BAH domain in complex with a nucleosome at 3.0 Å resolution. Science, 334(6058), 977–82. PMCID: PMC4098850

We have recently characterized some of the most fundamental mechanisms of PRC2 regulation. In this work, we studied the differences between EZH1 and EZH2 paralogs of catalytic subunit of PRC2. We used biochemical and cellular assays to show that single residue differences in these paralogs have large impact on the allosteric stimulation and response to competitive inhibitors. Additionally, we characterized the mechanism of PRC2 stimulation by a co-factor AEBP2.

Lee CH, Holder M, Grau D, Saldaña-Meyer R, Yu JR, Ganai RA, Zhang J, Wang M, LeRoy G, Dobenecker MW, Reinberg D, **Armache KJ**. (2018). Distinct stimulatory mechanisms regulate the catalytic activity of Polycomb Repressive Complex 2. Molecular Cell, 70(3):435-448. PMID: 29681498

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/karim.armache.1/bibliograpahy/45957662/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 GM115882 (PI) 07/01/2015 – 06/30/2020
Structural and functional analysis of gene silencing
The major goal of this project is to understand the mechanism of gene silencing in model organisms. We are studying silencing by Sir3 as part of SIR complex and of S. pombe HP1 protein Swi6.

Packard Fellowship for Science and Engineering (PI) 11/05/2015 - 11/04/2020
Transcription through the nucleosome: resolving the paradox
The major goal of this proposal is to visualize using structural biology methods RNA Polymerase II transcribing thorough nucleosomes.

Completed Research Support

Kimmel Scholar Award Armache (PI) 07/01/2014 – 06/30/2016
Structure and mechanism of PRC2 in cancer
The major goal of this proposal is to unravel the structure and mechanism of histone H3K27 methyltransferase complex Polycomb Repressive Complex II

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Stephen Abini-Agbomson

eRA COMMONS USER NAME (credential, e.g., agency login): SAA717

POSITION TITLE: Graduate Student

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Connecticut, Storrs CT	B.S.	05/2017	Structural Biology/Biophysics
New York University, New York NY	Ph.D.	-	Structural Biology

A. Personal Statement

DNA replication is one of the most fundamental processes in multicellular organisms. Initiation of replication is highly regulated and the detailed mechanisms in play at this step vary in different eukaryotes. In all eukaryotes this process involves the six subunit Origin Recognition Complex (ORC) binding to regions of the chromosome (origins) to recruit other components of the replication machinery. Origins have been mapped in the genome and their interactions with ORC are well understood in *Saccharomyces cerevisiae*. In this organism the ORC binds to DNA in a sequence specific manner. However, efforts to identify a consensus sequence responsible for ORC recruitment have not been successful in other yeast species and metazoans. One reason for this could be the variations in eukaryotic chromatin architectures. Specifically it has been hypothesized that direct interactions with nucleosomes and histone modifications might play an important role in origin selection in these species. My research aims to understand the evolutionary changes that have led to the divergence of eukaryotic origin association in a chromatin context using structural biology techniques like cryo-electron microscopy and X-ray crystallography.

B. Positions and Honors

2016 UCONN McNair Scholars Program-Fellow
2013-2017 UCONN Louis Stokes Alliance for Minority Participation (LSAMP)-Scholar

C. Contributions to Science

Korza, G., **Abini-Agbomson, S**., Setlow, B., Shen, A., & Setlow, P., Levels of L-malate and other low molecular weight metabolites in spores of Bacillus species and Clostridium difficile. PloS one (2017).

D. Additional Information: Research Support and/or Scholastic Performance

Research Support

NIH T32 Training Grant