BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

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NAME	POSITION TITLE
Hee-Sook Kim	Assistant Professor, Public Health Research Institute, Rutgers NJMS (Dept. of Microbiology, Biochemistry and Molecular Genetics)
eRA COMMONS USER NAME KHEE-SOOK	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Seoul Women's University, Seoul, South Korea	B.S.	1988 – 1992	Chemistry
Seoul Women's University, Seoul, South Korea	M.S.	1992 – 1994	Chemistry
Rutgers University, New Jersey, USA (Dr. Steven Brill lab)	Ph.D.	1997 – 2003	Molecular Biology and Biochemistry

A. PERSONAL STATEMENT

I have been trained in yeast genetics (Ph.D.) and trypanosome molecular biology (postdoctoral studies and since 2015, as an independently funded group leader). I work with the African trypanosome (*Trypanosoma brucei*) and my long-term focus has been on how trypanosomes maintain and diversify genetic information, with special interest on the mechanism of antigenic variation and potential pharmacological implications for the treatment of this neglected tropical disease.

Genes in *T. brucei* are organized in Polycistronic Transcription Units (PTUs), each of which contains over 100 genes on average. A few years ago, Tiengwe *et al* (*Cell Rep*., 2012) discovered that PTU transcription start sites in *T. brucei* were also locations of occupancy of the Origin Recognition Complex (ORC), which initiates DNA replication. This peculiar genome organization and dual usage of the same sites for replication and transcription indicates that there must be a close functional link between replication and transcription in *T. brucei*. While presumed co-ordination between transcription and replication must be crucial in *T. brucei* (where, because of PTU organization, even 'one' dysfunctional start site can affect the expression of > 100 genes), this coordination is not unique: In humans, ORC1 also binds many transcription start sites, and the timing of origin activation can correlate with transcription activity (Dellino *et al Genome Res*., 2013), suggesting that certain core generic features are shared between different organisms in coordinating replication and transcription. In this context, **first,** I aim to understand functional interactions between replication, transcription and chromatin factors in maintaining genome integrity and then to apply knowledge obtained from those studies to identify small molecules that selectively inhibit trypanosome specific elements. A **second** long-term interest of mine relates to genomic manipulation by *T. brucei,* specifically its mechanism of antigenic variation. The parasite takes advantage of 'unstable' genomic locations for diversification of its *V*ariant *S*urface *G*lycoprotein (*VSG)* genes, which is essential for the immune evasion of the parasite.

This proposal aims to understand dynamic interaction of chromatin structure with DNA replication and transcription, and their inter-dependent relationships, all of which are essential for trypanosome cell proliferation. My extensive expertise in the area of chromosome integrity and the strong support from my collaborators are integral to the success of this project. Together, our studies will provide valuable insights into *T. brucei* genome and epigenome duplication and control.

B. POSITIONS AND HONORS

Position and employment

3/1/2018 –	Assistant Professor, Public Health Research Institute, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, NJ
12/01/2017 – 2/28/2018	Assistant Professor Research, Cleveland State University, Cleveland, OH
2012 – 11/31/2018	Senior Research Associate, Laboratory of Lymphocyte Biology, Rockefeller University, New York, NY (Dr. Nina Papavasiliou lab)
2007 – 2012	Research Associate & Postdoctoral fellow, Laboratory of Molecular Parasitology Rockefeller University, New York, NY (Dr. George Cross lab)
2003 – 2007	Postdoctoral fellow, Dept. of Chromosome Biology, Memorial Sloan-Kettering Cancer Center, New York, NY (Dr. John Petrini lab)

Awards and Fellowships

2008	Rockefeller University Women in Science Fellowship

C. CONTRIBUTION TO SCIENCE

1. **DNA replication and recombination factors in chromosome break and genome integrity.** Chromosome instability is a hallmark of cancer. Proteins involved in DNA replication, recombination, repair, and DNA-damage response are essential in maintaining genome integrity in yeasts as well as in higher eukaryotes. Using the budding yeast *Saccharomyces cerevisiae* as a model organism, I discovered that Replication Protein A is important for DNA damage response as a sensor of damaged lesion through protein modification and specific interaction with replication and checkpoint proteins (Kim *et al* 2001 & 2003) and discovered a mechanistic details between functionality and protein-protein interaction (*e.g*. interaction of RPA with DNA2 and SAE2 oligomerization in their functions during replication and recombination) (Bae *et al* 2003, Kim *et al* 2008). These studies led to fundamental understanding on the roles of replication and recombination proteins in the pathways of cell cycle checkpoints and DNA damage response, dysfunction of which result in chromosome rearrangement and malignancy.

    1) **Kim HS** and Brill, SJ (2001) Rfc4 interacts with Rpa1 and is required for both replication and DNA damage checkpoints in *Saccharomyces cerevisae*. *Molecular Cellular Biology* 21(11), 3725-37 PMC87010
    2) Bae KH, **Kim HS**, Bae SH, Kang HY, Brill S, and Seo YS (2003) Bimodal interaction between replication-protein A and Dna2 is critical for Dna2 function both *in vivo* and *in vitro*. *Nucleic Acids Research* 31(12), 3006-15 PMC162255
    3) **Kim HS** and Brill, SJ (2003) *MEC1*-dependent phosphorylation of yeast RPA1 *in vitro*. *DNA Repair* 2(12), 1321-35 PMID: 14642562 “PMC Journal – In Process”
    4) **Kim HS**, Vijayakumar S, Reger M, Harrison J, Haber JE, Weil C, and Petrini JH (2008) Functional interactions between Sae2 and the Mre11 complex. *Genetics* 178, 711-723 PMC2248341

2. **Recombination of antigen gene family in host-pathogen interaction**. Chromosome rearrangement by DNA recombination is a common mechanism used by various pathogens for evading host immunity. With a firm working knowledge of chromosome integrity from a mechanistic point of view obtained from my earlier training, I focused on developing new approaches for understanding host-pathogen interactions. Allelic exclusion and switching of surface antigen genes in *T. brucei* are controlled by heterochromatic gene silencing and chromosome rearrangement within subtelomeric environments. One antigen switching mechanism occurs via DNA recombination at subtelomeric hotspots. I therefore initiated a bioinformatic search for several key proteins involved in recombination and replication and investigated their roles in antigen switching. I discovered that multiple recombination pathways are required for antigen switching and that telomere replication may have roles in triggering particular switches

1) **Kim HS** and Cross GA (2010) TOPO3α influences antigenic variation by monitoring Expression-Site-associated VSG switching in *Trypanosoma brucei*. *PLoS Pathogens* Jul 8; 6(7):e1000992 PMC2900300
2) **Kim HS** and Cross GAM (2011) Identification of *Trypanosoma brucei* RMI1/BLAP75 homologue and its roles in antigenic variation. *PLoS ONE* 6(9):e25313. PMC3182221

3. **DNA replication, gene expression, chromatin structure in *T. brucei***. DNA replication plays a pivotal role in maintaining genome integrity. *T. brucei* replication is poorly understood, therefore, as a start point, I characterized function of *Tb*ORC1 in DNA replication as well as in telomeric *VSG* gene silencing in collaboration with Drs. Li and Klingbeil. Although DNA replication proteins have been shown to have phenotypes in heterochromatic gene silencing, it is not mechanistically evident whether the loss-of-silencing phenotype in replication mutants is a direct outcome of chromatin structure changes. Interestingly, I cloned *Tb*MCM-BP from a loss-of-*VSG* silencing screen (in collaboration with Dr. Arthur Günzl, Kim *et al* 2013) and further discovered that MCM-BP functions in transcription termination where specific chromatin marks (H3v, H4v, base J) are associated. Furthermore, studies with chromatin marks revealed that locus-specific chromatin marks have important roles in DNA replication as well as transcription termination and initiation. Series of these discoveries led to a model that tripartite interaction between chromatin structure, replication, and transcription is essential in the maintenance of genome integrity in *T. brucei*.

   1) **Kim HS***, Park S-H, Günzl A, and Cross GA (2013) MCM-BP is required for repression of life-cycle specific genes transcribed by RNA polymerase I in the mammalian infectious form of *Trypanosoma brucei. PLoS ONE* 8(2):e57001. PMC3581582 (***corresponding**)
   2) Schulz D, Mugnier MR, Paulsen EM, **Kim HS**, Chung CW, Tough DF, Rioja I, Prinjha RK, Papavasiliou FN, and Debler EW (2015) Bromodomain Proteins Contribute to Maintenance of Bloodstream Form Stage Identity in the African Trypanosome *PLoS Biol*. 13(12):e1002316. PMC4672894
   3) Schulz D, Zaringhalam M, Papavasiliou FN and **Kim HS*** (2016) Base J and H3.V regulate transcriptional termination in *Trypanosoma brucei*. *PLOS Genetics* 12(1):e1005762 PMID: 26796638 (***corresponding**)
   4) **Kim HS** (2018) Genome-wide function of MCM-BP in *Trypanosoma brucei* DNA replication and transcription. *Nucleic Acids Research* PMID: 30407533 DOI: 10.1093/nar/gky1088

4. **VSG expression and antigenic variation**. *T. brucei* antigenic variation shares mechanistic features with many classic monoallelic gene expression systems both in pathogenic and non-pathogenic organisms and also with malignancy caused by instability of chromosome, especially in the realms of telomere biology, gene expression, chromatin modification, and chromosome rearrangement. To understand antigenic variation, I got involved in three main topics, including the development of genetic tools to study antigenic variation, identification of VSG sequence repertoire in the genome, and determination of VSG structure. Although *T. brucei* has a great potential in many research areas as a model organism, genetic and technical tools have been lacking, compared to other model organism. To improve and develop broadly useful tools trypanosome research, I focused on developing large-scale mutant screening method as well as developing convenient way of generating a cell line with multiple genes knocked out simultaneously (Kim et al 2013) and generating an overexpression ORF library (this ORF library was used for verification of our dual reporter line and will be used in the screen). The transposon mutagenesis screen identified several mutants and study of one of mutants discovered that replication protein MCM-BP is important for transcriptional silencing of genes transcribed by RNA pol I, including the coat protein gene VSGs. Additionally, I participated in the *VSG*nome and VSG structure projects (Cross *et al* 2014; Pinger *et al* 2018).

   1) Cross GAM, **Kim HS**, and Wickstead B (2014) Capturing the variant surface glycoprotein repertoire (the *VSG*nome) of *Trypanosoma brucei* Lister 427. *Molecular Biochemical Parasitology.* doi: 10.1016 PMID: 24992042 “PMC Journal – In Process”
   2) **Kim HS***, Li Z, Boothroyd C, and Cross GAM (2013) Strategies to construct null and conditional null *Trypanosoma brucei* mutants using Cre-recombinase and loxP. *Molecular Biochemical Parasitology*

191(1):16-19. PMC3830529 (***corresponding**)

3) Pinger J, Nešić D, Ali L, Aresta-Branco F, Lilic M, Chowdhury S, **Kim HS**, Verdi J, Raper J, Ferguson MAJ, Papavasiliou FN, Stebbins CE (2018) African trypanosomes evade immune clearance by O-glycosylation of the VSG surface coat. *Nature Microbiology* Aug:3(8):932-938 PMCID 6108419

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/heesook.kim.1/bibliograpahy/48426122/public/?sort=date&direction=descending

D. Research Support

Ongoing

1 R01 AI127562-01A1 (Kim), NIH/NIAID 08/01/17 – 7/31/22
Title: Molecular dynamics of genome and epigenome integrity in *Trypanosoma brucei*
Goal: The major goal is to study roles of chromatin factors in genome integrity in *T. brucei*.
Role: Principal Investigator

Completed in the last 2 years

1 R21 AI113419-01A1 (Kim, Schulz, Hovel-Miner), NIH/NIAID 02/01/15 – 1/31/17
Title: Generation, characterization and validation of a *T. brucei* overexpression library.
Goal: The major goal is to make highest quality well-controlled overexpression library to be used by everyone in the field.
Role: Principal Investigator (contact PI)