BIOGRAPHICAL SKETCH

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NAME: Baek Kim

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

POSITION TITLE: Professor and Director

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
Kyung-Hee University (Seoul, South Korea)	BS/RPh	3/1982	Pharmacy
Yon-Sei University (Seoul, South Korea)	MS	6/1987	Biochemistry
University of Arizona (Tucson, Arizona)	PhD	5/1993	Biochemistry
University of Washington (Seattle, Washington)	Postdoc	6/1997	Biochemistry/Virology

A. Personal Statement

My current research focuses are: 1) HIV-1 replication, mutagenesis, and evolution, 2) establishment of long-living HIV-1 myeloid reservoirs, 3) role of SAMHD1 in HIV biology. I was trained in the research field of the DNA-protein interactions, particularly with transcriptional repressors and DNA polymerases involved in DNA repair and DNA replication. I initiated my own research career using HIV-1 as a model to study roles of DNA polymerases in genomic mutagenesis and evolution, which was supported by various HIV/AIDS related research funding sources. This research activity led me to reveal that cellular dNTP levels play a significant role in HIV-1 replication kinetics and mutagenesis particularly in nondividing macrophages that are a key long living HIV reservoir and contribute to HIV-1 persistence. This research outcome has been helping many collaborators to elucidate the action mechanisms of a nondividing cell specific anti-HIV restriction factor, SAMHD1, which depletes cellular dNTPs in nondividing cells and kinetically suppress HIV-1 replication in nondividing viral target cell types. We also identified a macrophage specific nucleotide pool that may contribute to HIV-1 mutagenesis and evolution as well as pathways that enable HIV-1 infected macrophages to display extended life span and to become long-living viral reservoirs. These research activities will elucidate evolutionary and pathological significance of HIV infection to nondividing myeloid cells, and then to discover new anti-HIV therapeutic strategies that can contribute to HIV cure.

B. Positions and Honors

Positions:

2013-present	Director, Center for Drug Discovery, Full Professor, Department of Pediatrics, Emory University, Atlanta, Georgia
2009-2013	Full Professor, Department of Microbiology & Immunology, University of Rochester, Rochester, New York.
2007-2013	Virology Investigator, The NY Influenza Center of Excellence
2005-2009	Associate Professor (with unlimited tenure), Department of Microbiology & Immunology, University of Rochester, Rochester, New York.
1998-2005	Assistant Professor, Department of Microbiology & Immunology, University of Rochester, Rochester, New York.
1996-1998	Acting Instructor, Department of Pathology, University of Washington, Seattle, WA

1993-1996	Senior Fellow (postdoctoral trainee), Department of Pathology, University of Washington, Seattle, WA.
1987-1993	Research Assistant, University of Arizona (Biochemistry), Tucson, Arizona.
1986-1987	Pharmacist (RPH), Yonsei Medical Center, Seoul, Korea
1983-1986	Clinical Flight Officer, Korean Air Force Aero-Medical Research Center.

Honors:

NIH AMCB (AIDS Molecular and Cellular Biology) study section, ad hoc, 2015
NIH AMCB (AIDS Molecular and Cellular Biology) study section, Regular member 2008~2012
NIH AARR Special Emphasis Panel, Basic Science for HIV-1 Cure, 2015
Amfar (American Foundation for AIDS Research) review, Basic Science for Cure, 2015
NIH AARR Special Emphasis Panel (Chair and member), 2012, 2013, 2014
NIH AARR Special Emphasis Panel, HIV Eradication U19, 2010
NIH ADDT (AIDS Discovery and Development Therapeutics) special emphasis study sections, 2006~
NIH F31 Diversity, Immunology study section ad hoc, 2007~
NY Influenza Center for Excellence, Virology co-investigator, 2008-2012
Developmental Center for AIDS Research, Virology Program Director, 2009~2012
AIDS Research Grant Award (1997), American Foundation for AIDS Research.
Best Thesis Award (1993), Department of Biochemistry, University of Arizona, Tucson, Arizona.
Graduation cum laude (1982), School of Pharmacy, Kyung-Hee University, Seoul, Korea.
Hyundai Corp. Full Scholarship Award (1978-1982), Kyung-Hee University, Seoul, Korea.

C. Contribution to Science

1) Unique Enzymological Properties of HIV-1 Reverse Transcriptase: This research interest focuses on the enzymological understanding of HIV reverse transcriptase (RT) and the mechanistic roles of the RT in HIV replication, evolution and cell tropism. My lab, *for the first time*, reported that HIV-1 RT is uniquely active even at low dNTP concentrations (nM range), and then we found that all lentivirus RTs that we tested displayed high polymerase activity at low dNTP concentrations while other retrovirus RTs (i.e. oncoretrovirus RTs) are active only at high dNTP concentrations (uM range). Further kinetic studies revealed that the lentivirus RTs have much higher binding affinity to dNTPs than the oncoretrovirus RTs, and we identified various residues of HIV-1 RT involved in the unique tight dNTP binding affinity of HIV-1 RT. This finding led us to hypothesize that the unique high dNTP binding affinity of lentivirus RTs may allow the lentiviruses to replicate efficiently in nondividing cells that have low cellular dNTP concentrations. We also reported that the dNTP binding affinity can vary even among lentivirus RTs, proposing that this RT enzyme kinetic variation may be linked to the dNTP concentration discrepancy between activated/dividing T cells and nondividing macrophages, and ultimately to viral cell tropism.

Weiss KK, Bambara RA, Kim B. Mechanistic role of residue Gln151 in error prone DNA synthesis by human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT). Pre-steady state kinetic study of the Q151N HIV-1 RT mutant with increased fidelity. *J Biol Chem.* 2002;277(25):22662-9.

Skasko M, Weiss KK, Reynolds HM, Jamburuthugoda V, Lee K, Kim B. Mechanistic differences in RNA-dependent DNA polymerization and fidelity between murine leukemia virus and HIV-1 reverse transcriptases. *J Biol Chem*. 2005;280(13):12190-200.

Diamond TL, Souroullas G, Weiss KK, Lee KY, Bambara RA, Dewhurst S, Kim B. Mechanistic understanding of an altered fidelity simian immunodeficiency virus reverse transcriptase mutation, V148I, identified in a pig-tailed macaque. *J Biol Chem.* 2003;278(32):29913-24.

Lenzi M Gina, Domaoal A Robert, Kim Dong-Hyun, Schinazi F Raymond, Kim Baek (2015) Kinetic variations between reverse transcriptases of viral protein X coding and noncoding lentiviruses. *Retrovirology.*11:111.

2) Cellular dNTP Concentrations and HIV-1 Replication Kinetics: In 2004, my lab developed a highly sensitive dNTP assay that, *for the first time*, enabled us to determine the dNTP concentration of terminally differentiated/nondividing human primary macrophages. The dNTP concentration in macrophages was extremely low (20-40nM), compared to activated/dividing CD4+ T cells (2-5uM). A series of our studies revealed that this low dNTP abundance in the nondividing HIV-1 target cells kinetically suppresses the reverse transcription of HIV-1 in nondividing cells, proposing that the low dNTP availability might have served as a

selective pressure to drive HIV-1 RT to bind to dNTP tightly in order to efficiently synthesize proviral DNA in the nondividing target cells.

Diamond TL, Roshal M, Jamburuthugoda VK, Reynolds HM, Merriam AR, Lee KY, Balakrishnan M, Bambara RA, Planelles V, Dewhurst S, Kim B. (2004) Macrophage tropism of HIV-1 depends on efficient cellular dNTP utilization by reverse transcriptase. *J Biol Chem.* 279(49):51545-53.

Jamburuthugoda VK, Chugh P, Kim B. Modification of human immunodeficiency virus type 1 reverse transcriptase to target cells with elevated cellular dNTP concentrations. *J Biol Chem.* 2006;281(19):13388-95.

Jamburuthugoda VK, Santos-Velazquez JM, Skasko M, Operario DJ, Purohit V, Chugh P, Szymanski EA, Wedekind JE, Bambara RA, Kim B. Reduced dNTP binding affinity of 3TC-resistant M184I HIV-1 reverse transcriptase variants responsible for viral infection failure in macrophage. *J Biol Chem.* 2008;283(14):9206-16.

Van Cor-Hosmer SK, Daddacha W, Kim B. Mechanistic interplay among the M184I HIV-1 reverse transcriptase mutant, the central polypurine tract, cellular dNTP concentrations and drug sensitivity. *Virology.* 2010;406(2):253-60.

3) SAMHD1, Cellular dNTP Concentrations and HIV-1 Reverse Transcription in Nondividing Myeloid Cells: In 2012, SAMHD1 was identified as a myeloid specific anti-HIV restriction factor, and Vpx of HIV-2 and many SIV strains counteracts the anti-viral activity of SAMHD1, which enhances the infectivity of the Vpx encoding lentiviruses to the nondividing myeloid cells. Our initial report revealed that SAMHD1, which is dNTPase, is responsible for the extremely low dNTP concentration of macrophages that we reported in 2004. Indeed, we observed that Vpx enhances lentivirus replication kinetics by elevating cellular dNTP concentrations in nondividing viral target cells such as macrophages, DCs and resting CD4+ T cells. We have been engaged in numerous collaborations for elucidating the SAMHD1-medaited and nondividing cell specific anti-HIV mechanisms (see **Progress Report**).

Lahouassa H*, Daddacha W*, Hofmann H, Ayinde D, Logue EC, Dragin L, Bloch N, Maudet C, Bertrand M, Gramberg T, Pancino G, Priet S, Canard B, Laguette N, Benkirane M, Transy C, Landau NR#, Kim B#, Margottin-Goguet F# (2012) SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. *Nat Immunol*. 13(3):223-8. *: Co-First Authors; #: Co-Communicating Authors.

Kim, B, Nguyen, L, Daddacha, W. Hollenbaugh, JA (2012) Tight Interplay Among SAMHD1 Level, Cellular dNTP Levels and HIV-1 Proviral DNA Synthesis Kinetics in Human Primary Monocyte-Derived Macrophages *J. Biol. Chem.* 287(26):21570-4

Amie SM, Bambara RA, Kim B. (2013) GTP is the Primary Activator of the Anti-HIV Restriction Factor SAMHD1. *J Biol Chem*. 2013 Jul 23. [Epub ahead of print].

Ryoo J, Choi J, Oh C, Kim S, Seo M, Kim SY, Seo D, Kim J, White TE, Brandariz-Nuñez A, Diaz-Griffero F, Yun CH, Hollenbaugh JA, Kim B, Baek D, Ahn K. (2014) The ribonuclease activity of SAMHD1 is required for HIV-1 restriction. *Nat Med*. 2014 doi: 10.1038/nm.3626.

4) Unique Nucleotide Pools in Macrophages and HIV-1 Mutagenesis: In 2010, *for the first time*, we reported that macrophages harbor unique nucleotide dNTP/rNTP pools. Unlike dNTPs, macrophages contain the same high levels of rNTPs (mM range) as dividing cells, presumably because macrophages still need rNTPs for transcription and energy metabolism (ATP). However, due to the extremely low dNTP concentration, macrophages have a greater concentration discrepancy between dNTPs and rNTPs, which forces HIV-1 RT to incorporate noncanonical rNTPs during reversion transcription. Since the rNTP incorporation during DNA synthesis is known to be mutagenic, we hypothesize that the unique macrophage nucleotide pool contributes to HIV-1 mutagenesis.

Kennedy EM, Gavegnano C, Nguyen L, Slater R, Lucas A, Fromentin E, Schinazi RF, Kim B. Ribonucleoside triphosphates as substrate of human immunodeficiency virus type 1 reverse transcriptase in human macrophages. *J Biol Chem*. 2010;285(50):39380-91. Selected as a “Must Read” paper by the Faculty of 1000 (F-1000).

Kennedy EM, Amie SM, Bambara RA, Kim B. (2012) Frequent incorporation of Ribonucleotides during HIV-1 reverse transcription and their attenuated repair in macrophages. J Biol Chem. 287(17):14280-8

Daddacha W, Noble E, Nguyen LA, Kennedy EM, Kim B (2013) Effect of Ribonucleotides Embedded in a DNA Template on HIV-1 Reverse Transcription Kinetics and Fidelity. *J. Biol. Chem.* 288(18):12522-32. PMID:

23479739.
Laura Nguyen, Robert A. Domaoal, Raymond F. Schinazi, Baek Kim (*2015*) Pre-steady State Kinetic Analysis of HIV-1 Reverse Transcriptase for Non-canonical Ribonucleoside Triphosphate Incorporation and DNA Synthesis from Ribonucleoside-containing DNA Template *Antiviral Research* 115:75-82.

5) Influenza virus RNA polymerase enzymology and virology: Using the support from NY Influenza Center of Excellence, we established robust expression system and enzyme assay for influenza RNA polymerase complex. This system enabled us to answer many biochemical questions that addressed important virological and evolutionary aspects of influenza viruses.

Aggarwal S, Bradel-Tretheway B, Takimoto T, Dewhurst S, Kim B. (2010) Biochemical characterization of enzyme fidelity of influenza A virus RNA polymerase complex. PLoS One.;5(4):e10372.

Aggarwal S, Dewhurst S, Takimoto T, Kim B. (2011) Biochemical impact of the host adaptation-associated PB2 E627K mutation on the temperature-dependent RNA synthesis kinetics of influenza A virus polymerase complex. J Biol Chem.;286(40):34504-13.

Noble E, Mathews DH, Chen JL, Turner DH, Takimoto T, Kim B. (2011) Biophysical analysis of influenza A virus RNA promoter at physiological temperatures. J Biol Chem.;286(26):22965-70.

Erin Noble, Andrew Cox, Jerome Deval, and Baek Kim (2012) Endonuclease Substrate Selectivity Characterized with Full-Length PA of Influenza A Virus Polymerase. Virology. 436(2):247-54

D. Research Support (Active Awards)

NIH R01 AI049781 (Kim) Dates: 04/01/12 – 3/31/17
NIH/NIAID (PI)
Replication Fidelity and Lentivirus Pathogenesis
Major goal: To examine the mechanism(s) whereby HIV-1 reverse transcriptase influences replication fidelity and pathogenesis.

NIH R01 GM104198 (Kim): Dates: 7/1/16 - 6/30/20
NIH/NIGMS (PI)
SAMHD1 controls dNTP pool and HIV sensitivity to NRTIs
Major goal: To elucidate roles of SAMHD1 in HIV sensitivity to NRTIs

NIH R01 GM105876 (Mansky/Peterson: subcontract, Kim) Dates: 9/15/2013 – 5/31/2017
NIH/NIGMS (Multiple PIs)
HIV Reverse Transcriptase–mediated mutagenesis (Subcontract from Univ. Minnesota)
Major goal: Finding chemicals to induce lethal mutagenesis

NIH 1R01MH100999 (Schinazi, Raymond F. and Tyor, William) Dates: 06/18/13 to 04/30/18
NIH/NIMH (Co-I)
Therapeutics Targeting Macrophages/Microglia to Eradicate CNS HIV-1 Reservoirs
Major goal: This study will investigate new adjunctive therapeutic strategies o target improved therapy to viral reservoirs in the central nervous system (i.e., mononuclear phagocytes, MP) and eliminate these reservoirs and/or reduce risk of developing HIV-1 associated neurocognitive disorders (HAND).

R01 (Kim, Co-Investigator) Dates: 9/1/16 -8/31/21
NIH/NIAID (Subcontract through Prime PI Diaz-Griffero – Albert Einstein COM)
Regulation of SAMHD1 antiviral activity
Major goal: This study will allow the careful characterization of the enzymatic parameters of SAMHD1 phosphorylation mutants.