
BIOGRAPHICAL SKETCH

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NAME: Bieker, James J

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

POSITION TITLE: Professor

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
St. Louis University, St. Louis, MO	BS in Chem	05/1974	Chemistry
Northwestern University, Evanston, IL	PhD	04/1981	Biochemistry
Washington University School of Medicine, St. Louis, MO, and The Rockefeller University, New York, NY	Postdoc	12/1985	Molecular Biology

A. Personal Statement

My lab discovered EKLF in 1992, and we have been actively pursuing the mechanism of its action using biochemical, molecular, cellular, and developmental approaches with NIH-funded studies ever since. EKLF is now the founding member (KLF1) of a family of seventeen proteins, some of which have been directly implicated in a range of normal and altered cellular control mechanisms. We have been particularly focused on illuminating EKLF-directed transcriptional and epigenetic controls that lead to regulated erythroid gene expression in both progenitors and late stages, and additionally in determining whether directed, quantitative control of its expression may enable its use in alleviation of hemoglobinopathies.

Our initial studies established the cognate DNA sequence and the role of EKLF as an activator of adult β -globin expression, demonstrated that β -thalassemia point mutations are not properly recognized by EKLF, showed that EKLF acts as a β -like globin switching factor in the red cell, and showed the surprising cell-restricted pattern of its expression during development. These have formed the basis for all subsequent studies by us and others on EKLF structure/function and regulation of downstream genes. EKLF is now recognized as a global regulator of erythroid gene expression.

1. I. J. Miller and **J. J. Bieker**, A Novel, Erythroid Cell-Specific Murine Transcription Factor That Binds to the CACCC Element and Is Related to the Krüppel Family of Nuclear Proteins. *Molecular and Cellular Biology*, **13**, 2776-2786 (1993). PMID: PMC359658.
2. W. C. Feng, C.M. Southwood, and **J. J. Bieker**, Analysis of β -Thalassemia Mutant DNA Interactions with EKLF, an Erythroid Cell-Specific Transcription Factor. *Journal of Biological Chemistry*, **269**, 1493-1500 (1994).
3. D. Donze, T. M. Townes, and **J. J. Bieker**, Role of Erythroid Krüppel-like Factor (EKLF) in Human γ - to β -Globin Switching, *Journal of Biological Chemistry*, **270**, 1955-1959 (1995).
4. C. M. Southwood, K. M. Downs, and **J. J. Bieker**, Erythroid Krüppel-like Factor (EKLF) exhibits an early and sequentially localized pattern of expression during mammalian erythroid ontogeny, *Developmental Dynamics*, **206**, 248-259 (1996).

B. Positions and Honors

Positions and Employment

1973-1974 Undergraduate Research Assistant with Dr. Thomas J. Curphey
Department of Chemistry, St. Louis University
1976-1981 Graduate Research Assistant with Dr. Lawrence B. Dumas

1981-1985 Department of Biochemistry and Molecular Biology, Northwestern University
 Postdoctoral Research Associate with Dr. Robert G. Roeder
 Department of Biological Chemistry, Washington University School of Medicine
 Laboratory of Biochemistry and Molecular Biology, The Rockefeller University

1986-1993 Assistant Professor

1994-1998 Associate Professor

1999-2001 Associate Professor with Tenure

2002-present Professor
 Department of Developmental and Regenerative Biology, The Mount Sinai School of Medicine

2004-present Black Family Stem Cell Institute
 The Mount Sinai School of Medicine

2006-2007 Interim Co-director, Black Family Stem Cell Institute, The Mount Sinai School of Medicine

2008-present Tisch Cancer Institute
 The Mount Sinai School of Medicine

Other Experience and Professional Memberships

1991-1995 Associate Editor, *The Journal of Experimental Zoology*

1998-2009 Ad hoc NIH Study Sections (Hem1, Hem2, HP, ELB, HT)

2000-2006 Career Development Program Subcommittee, Leukemia & Lymphoma Society

2005-2008 Editorial Board, *Molecular and Cellular Biology*

2007/2009 Vice-Chair/Chair, "Red Cell" Gordon Research Conference

2009-2013 Member, ELB (now MCH) NIH Study Section

2015,18,20 Special Emphasis Panel, ZRG1, NIH

2017/2018 Vice-Chair/Chair, Committee on Red Cell Biology, American Society of Hematology

Honors

1973 Monsanto Summer Research Fellowship

1974 Leopold Marcus Award for Research in Chemistry

1974 Pi Mu Epsilon Honorary Mathematics Fraternity

1994-1999 Scholar of the Leukemia Society of America

2006 Visiting Scientist, Weatherall Institute of Molecular Medicine, Oxford University, Oxford UK

2008 Tohoku Medical Society Testimonial, Tohoku University, Sendai, Japan

2012 Keynote Speaker, FASEB Conference on the Biology and Pathobiology of Krüppel-like Factors, Snowmass Village, CO

2013 Faculty Council Award for Academic Excellence

2018 Guest Speaker, Scientific Program on Red Cell Biology, American Society of Hematology, San Diego, CA

C. Contribution to Science [all of the following have been supported by funds for me as PI]

1. Although our initial studies focused on characterizing EKLF's role in transcriptional activation of β -globin expression, it became clear that it also plays a role in the epigenetic profile of the locus by interacting with histone acetyltransferase and chromatin remodeling proteins. Many groups have been built upon these observations to show that EKLF is critical for forming the 3-dimensional structure of the locus. Importantly, our studies also showed that EKLF itself becomes modified as a result of these interactions, and that these alterations can have a direct effect on protein-protein interactions (also see below).
 - a. W. Zhang and **J. J. Bieker**, Acetylation and modulation of Erythroid Krüppel-like Factor (EKLF) activity by interaction with Histone Acetyltransferases, *Proceedings of the National Academy of Sciences*, 95, 9855-9860 (1998). PMCID: PMC21426.
 - b. W. Zhang, S. Kadam, B. M. Emerson, and **J. J. Bieker**, Site-Specific Acetylation by p300/CBP Regulates Erythroid Krüppel-like Factor (EKLF) Transcriptional Activity via its Interaction with the SWI/SNF Complex, *Molecular and Cellular Biology*, 21, 2413-2422 (2001). PMCID: PMC86874.
 - c. T. Sengupta, K. Chen, E. Milot, and **J. J. Bieker**, Acetylation of EKLF is essential for epigenetic modification and transcriptional activation of the β -globin locus, *Molecular and Cellular Biology*, 28, 6160-6170 (2008). PMCID: PMC2577412.

- d. S. Soni, N. Pchelintsev, P.D. Adams, and **J.J. Bieker**, Transcription factor EKLF (KLF1) recruitment of the histone chaperone HIRA is essential for β -globin gene expression, *Proceedings of the National Academy of Sciences*, 111, 13337-13342 (2014). [highlighted in *Hematopoiesis News*]. PMID: PMC4169976
2. EKLF remained recognized for its red cell-restricted expression, where it plays a positive role in early and late stages of erythropoiesis. However, an unexpected observation was that we found it also plays a role in the bipotential decisions emanating from the megakaryocyte-erythroid progenitor by repressing megakaryopoiesis, with its sumoylation status being critical for this effect. Others have built upon these studies to postulate that EKLF-deficient red cells exhibit an 'identity crisis', expressing a mix of meg and erythroid markers. These expression surprises have continued, as we showed that along with the differentiating erythroid cell it is also expressed in the central macrophage (but not other macrophage) of the erythroblastic island.
- a. M. P. Frontelo*, D. Manwani*, M. Galdass, H. Karsunky, F. Lohmann, P. G. Gallagher, and **J. J. Bieker**, Novel role for EKLF in megakaryocyte lineage commitment, *Blood*, 110, 3871-3880 (2007). [*co-first authors] [highlighted as an *Inside Blood* preview]. PMID: PMC2190608.
 - b. F. Lohmann and **J. J. Bieker**, Activation of Ekf expression during hematopoiesis by Gata2 and Smad5 prior to erythroid commitment, *Development*, 135, 2071-2082 (2008). [highlighted as an *In this Issue* preview].
 - c. L. Xue, M. Galdass, M.N. Gnanapragasam, D. Manwani, and **J.J. Bieker**, Extrinsic and intrinsic control by EKLF (KLF1) within a specialized erythroid niche, *Development*, 141, 2245-2254 (2014). PMID: PMC4034424.
 - d. M.N. Gnanapragasam, K.E. McGrath, S. Catherman, L. Xue, J. Palis, and **J.J. Bieker**, EKLF/KLF1-regulated cell cycle exit is essential for erythroblast enucleation, *Blood*, 128, 1631-1641 (2016). [highlighted in *Hematopoiesis News*]. PMID: PMC5034741.
3. In collaboration with Dr L Peters we characterized the neonatal anemia (*Nan*) mutation that maps to murine EKLF and found unusual molecular properties that partly explain the altered genetic output of the *Nan*/+ red cell. The remains an activate area for our labs as well as others, as its mechanism of effect, seen even in the presence of a wild type EKLF copy, is enigmatic. In collaboration with Dr D Manwani, we determined the mutation that leads to a subtype of congenital dyserythropoietic anemia (CDA) to the same residue in human EKLF as had been found in the mouse *Nan* mutation. In combination with studies from other groups, this is now accepted as CDA Type IV. The resultant molecular, genetic, and biochemical changes remain of high interest to decipher.
- a. M. Siatecka, K.E. Sahr, S.G. Andersen, M. Mezei, **J.J. Bieker***, and L.L Peters*, Severe anemia in the *Nan* mutant mouse caused by sequence-selective disruption of erythroid Krüppel-like factor, *Proceedings of the National Academy of Sciences*, 107, 15151-15156 (2010). [*co-corresponding authors] [highlighted in *Hematopoiesis News*; highlighted in *Health and Medicine Week*]. PMID: PMC2930539.
 - b. J.A. Jaffray, W.B. Mitchell, M.N. Gnanapragasam, S.V. Seshan, X. Guo, C.M. Westoff, **J.J. Bieker**, and D. Manwani, Erythroid Transcription Factor EKLF/KLF1 Mutation Causing Congenital Dyserythropoietic Anemia Type IV in a Patient of Taiwanese Origin: Review of all reported cases and development of a clinical diagnostic paradigm, *Blood Cells, Molecules, and Diseases*, 51, 71-75 (2013). PMID: PMC4560093
 - c. A. Planutis, L. Xue, C.D Trainor, M. Dangeti, K. Gillinder, M. Siatecka, L.L. Peters, A.C. Perkins, **J.J. Bieker**, Neomorphic effects by the *neonatal anemia* (*Nan*-EKLF) mutation contribute to systemic deficits in development, *Development*, 144, 430-440 (2017). [highlighted as an *In this Issue* preview; highlighted in *Hematopoiesis News*]. PMID: PMC5341802
 - d. L. Varricchio, A. Planutis, D. Manwani, J. Jaffray, W.B. Mitchell, A.R. Migliaccio*, and **J.J. Bieker***, Genetic disarray follows mutant KLF1-E325K expression in a congenital dyserythropoietic anemia patient, *Haematologica*, 104, 2372-2381 (2019). [*co-corresponding authors] [highlighted in *Hematopoiesis News*]
4. Our observations on the cell-restricted expression pattern of EKLF immediately raised questions about the mechanism of this tight control. We analyzed its promoter and chromatin structure by in vitro and in vivo approaches, identified a strong enhancer, and used differentiating embryonic stem cells to identify the extracellular effectors of its expression during development. These studies form the basis for experiments

that aim to quantitatively decrease levels of EKLF, as it has been shown (by others) that haploinsufficient levels are sufficient to dysregulate the human β -like globin locus, resulting in a therapeutically useful increase in γ - and/or ϵ -globin expression in the adult red cell.

- a. X. Chen, M. Reitman, and **J. J. Bieker**, Chromatin structure and transcriptional control elements of the Erythroid Krüppel-like Factor (EKLF) gene, *Journal of Biological Chemistry*, 273, 25031-25040 (1998).
 - b. C. A. Adelman, S. Chattopadhyay, and **J. J. Bieker**, The BMP/BMPR/Smad Pathway Directs Expression of the Erythroid-Specific EKLF and GATA1 Transcription Factors During Embryoid Body Differentiation in Serum-free Media, *Development*, 129, 539-549 (2002).
 - c. F. Lohmann and **J. J. Bieker**, Activation of Ekf expression during hematopoiesis by Gata2 and Smad5 prior to erythroid commitment, *Development*, 135, 2071-2082 (2008). [highlighted as an *In this Issue* preview]
 - d. F. Lohmann*, M. Dangeti*, S. Soni, X. Chen, A. Planutis, M.H. Baron, K. Choi, and **J.J. Bieker**, The DEK oncoprotein is a critical component of the EKLF/KLF1 enhancer in erythroid cells, *Molecular and Cellular Biology*, 35, 3726-3738 (2015). [*co-first authors] [highlighted in *Exp Hem* 43, 827 (15)]. PMID: PMC4589598.
5. Yet another unexpected observation followed from the finding that EKLF interacts with corepressor proteins. Interestingly, the modification status of EKLF plays a critical role here as it does with its coactivator interactions (noted above). In this case, site-specific acetylation and sumoylation enable interactions with Sin3a, HDAC1, and Mi2 β . Although the strongest results of these changes appear related to meg/erythroid bipotential decision making (described above) and to primitive/definitive erythropoiesis, specific repression targets have remained elusive. As a result, any of the global red cell analyses performed by us and others keep these complexities in mind.
- a. X. Chen and **J. J. Bieker**, Unanticipated Repression Function Linked to Erythroid Krüppel-like Factor (EKLF), *Molecular and Cellular Biology*, 21, 3118-3125 (2001). PMID: PMC86939.
 - b. X. Chen and **J. J. Bieker**, Stage-specific Repression by the EKLF Transcriptional Activator, *Molecular and Cellular Biology*, 24, 10416-10424 (2004). PMID: PMC529052.
 - c. M. Siatecka, L. Xue, and **J. J. Bieker**, Sumoylation of EKLF Promotes Transcriptional Repression and Is Involved in Inhibition of Megakaryopoiesis, *Molecular and Cellular Biology*, 27, 8547-8560 (2007). PMID: PMC2169404.
 - d. M. Siatecka, S. Soni, A. Planutis, and **J.J. Bieker**, Transcriptional activity of EKLF/KLF1 modulated by PIAS3, *Journal of Biological Chemistry*, 290, 9929-9940 (2015). PMID: PMC4392289.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/james.bieker.1/bibliography/40735946/public/?sort=date&direction=descending>

D. Research Support

Ongoing Research Support

R01 DK46865-27 (J.J. Bieker, PI)

8/1/93-3/31/21

Function of a Putative Determinant in Hematopoiesis

Investigation of molecular and biological function of EKLF/KLF1 with respect to its ability to coordinate histone presence and transcriptional activation at target sites, and how selected mutations in human and mouse KLF1 alter this regulation.

R01 HL134684-03 (J.J. Bieker and A.R. Migliaccio, multi-PI)

9/20/18-5/31/22

Generation of cultured RBCs with rare phenotypes for transfusion from sources usually discarded during regular blood donations

Development of new ways to efficiently produce cultured red blood cells and provide novel insights into the mechanisms that regulate their proliferation/differentiation.

Doris Duke Charitable Foundation (J.J. Bieker and J.A Glassberg, dual-PI) 9/1/19-8/31/22
Quantitative modulation of an erythroid regulator as a novel genetic target for sickle cell disease
Addressing whether a gene editing approach directed at quantitatively modifying the levels of the EKLF/KLF1 transcription factor will provide a novel means to increase fetal globin levels and alleviate the morbidity and mortality associated with sickle cell disease.

R01 DK121671-01 (J.J. Bieker, PI) 4/15/20-1/31/24
Coordinate regulation of erythroid and macrophage lineages in development by EKLF/KLF1
Investigating the role of EKLF/KLF1 in the erythroid-myeloid progenitor and in macrophage identity and function in the erythroblastic island.

Completed Research Support (past 3 yrs)

R01/R56 DK102260 (J.J. Bieker, PI) 4/1/14-6/30/19
Intrinsic and extrinsic control of erythropoietic maturation
EKLF's coordinating role in erythroid terminal maturation events.