BIOGRAPHICAL SKETCH

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NAME: Sandell, Linda

eRA COMMONS USER NAME (agency login): sandelll

POSITION TITLE: Professor and Co-Director, Musculoskeletal Research Center

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Denver University, Denver, CO	BA	1969	Zoology
Denver University, Denver, CO	MS	1971	Biological Sciences
Northwestern University (Dr. A. Veis), Chicago, IL	PH.D.	1980	Biochemistry
University of Chicago (Dr. A. Dorfman), Chicago, IL	Post-doc	1982	Molecular Biology

A. PERSONAL STATEMENT

I directed the NIAMS P30 Core Center for Musculoskeletal Biology and Medicine from 2009-2017, and continue to serve as an advisor to the current Director, Dr. Silva, and the other Directors. (http://musculoskeletalcore.wustl.edu/home.aspx). I have expertise and leadership as a Cell and Molecular Biologist and as a Biochemist. During the past four decades I have led and completed many research projects, most of which were funded by the NIH/NIAMS (continuous funding since 1982). During this process I have mentored over 50 undergraduates, graduate students, postdoctoral fellows as well as clinical trainees (surgical fellows in Orthopaedic Surgery). I currently mentor post and pre doctoral student whenever the opportunities arise. My experiences have allowed me to develop and guide diverse interdisciplinary areas of research that have allowed me and my laboratory to contribute and expand knowledge in the fields of chondrogenesis, skeletal development, and osteoarthritis using human as well as animal models.

Recent publications most relevant to this proposal:

1. Rai, M. F., Tycksen, E. D., **Sandell, L. J.,** Brophy, R. H. Advantages of RNA-seq compared to RNA microarrays for transcriptome profiling of anterior cruciate ligament tears. J Orthop Res. doi: 10.1002/jor.23661. **2017**
2. Rai, M. F., Duan, X., Quirk, J. D., Holguin, N., Schmidt, E.J, Chinzei, N., Silva, M. J., **Sandell, L.J.** Post-Traumatic Osteoarthritis in Mice Following Mechanical Injury to the Synovial Joint. Sci Rep. Mar 27;7:45223. **2017**
3. Yan, H., Duan, X., Pan, H., Holguin, N., Rai, M. F., Akk, A., Springer, L. E., Wickline, S. A., Sandell, L. J., Pham, C. T. Suppression of NF-κB activity via nanoparticle-based siRNA delivery alters early cartilage responses to injury. Proc Natl Acad Sci U S A. Oct 11;113(41):E6199-E6208. **2016**
4. Takebe, K., Rai, M. F., Schmidt, E. J., **Sandell, L. J.** The chemokine receptor CCR5 plays a role in post-traumatic cartilage loss in mice, but does not affect synovium and bone. Osteoarthritis Cartilage. Mar;23(3):454-61. **2015**

B. POSITIONS AND HONORS

Positions and Employment

1982 - 1987	Assistant Professor, Departments of Biochemistry and Orthopedic Surgery and Division of Cell Biology, Rush Medical College, Chicago, IL
1987 - 1993	Associate Professor, Department of Orthopaedics, University of Washington, Seattle, WA
1987 - 1997	Faculty, Cell and Molecular Biology Training Program, University of Washington, Seattle, WA
1988 - 1993	Adjunct Associate Professor, Department of Biochemistry, Univ. of Washington, Seattle, WA
1990 - 2001	Research Career Scientist, Department of Veterans Affairs, Univ. of Washington, Seattle, WA
1993 - 1997	Adjunct Professor, Department of Biochemistry, University of Washington, Seattle, WA

1993 - 1997	Professor, Department of Orthopaedics, University of Washington, Seattle1, WA
1997 -	Professor, Department of Cell Biology and Physiology, Washington University School of Medicine,, St. Louis, MO
1997 -	Professor and Director of Research, Department of Orthopaedic Surgery, Washington University School of Medicine, , St. Louis, MO
1998 -	Member, Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO
2008 -	Mildred B. Simon Professor of Orthopaedic Surgery, Washington University School of Medicine, St. Louis, MO
2009 -2017	Director, Core Center for Musculoskeletal Biology and Medicine, Washington Unviersity School of Medicine, St. Louis, MO
2011 –	Adjunct Professor, Department of Biomedical Engineering, Washington University School of Medicine, St. Louis, MO

2014-2019, Editor in Chief, Journal of Orthopaedic Research

Other Experience and Professional Memberships

1980 -	Member, American Association for the Advancement of Science
1980 -	Member, Sigma Xi Research Society
1983 -	Member, Orthopaedic Research Society
1985 -	Member, American Society for Cell Biology
1987 -	Member, American Society of Biochemistry and Molecular Biology
1996 -	Member, The Histochemical Society
1998 -	Member, American Academy of Orthopaedic Surgeons
2000 -	Member, American Association of Anatomists
2000 -	Member, Stem Cell Society
2000 -	Member, Osteoarthritis Research Society International
2000 -	Member, RNA Society
2005 -	Member, International Cartilage Repair Society

Honors

1992	Kappa Delta Award for Basic Research in the Musculoskeletal System, American Association of Orthopaedic Surgeons (AAOS)
1995	Chair, Collagen Gordon Conference
1999	President, Orthopaedic Research Society, Board of Directors: 1995-2001
1998	Chair, Bioengineering and Orthopaedic Sciences Gordon Conference
1998	Advisory Council, National Institute for Arthritis and Musculoskeletal and Skin Diseases
2001	ISTO Technologies - 2001 - 2006, Scientific Advisory Board
2003	Co-Chair and Founder, Gordon Conference, Biology and Pathology of Cartilage
2005	Co-Chair and Founder, , Gordon Conference, Biology and Pathology of Cartilage
2005	President 2005 - 2006, American Society for Matrix Biology
2007	President - 2007- 2008, Histochemical Society
2008	Chair 2008 - 2011, Orthopaedic Research and Education Foundation, Basic Science Grant Review Committee
2010	Women's Leadership Award, Orthopaedic Research Society
2011	President 2011 - 2013, Osteoarthritis Research Society International
2014	Medical/Research Honoree, Arthritis Foundation Silver Ball
2015	Alfred E. Shands Award, Orthopaedic Research Society
2016	Distinguished Investigator Award, Orthopaedic Research Society
2016	Lifetime Achievement Award, Osteoarthritis Research Society International
2017	Lifetime Achievement Award, International Cartilage Repair Society

C. Contribution to Science

1. Type II procollagen gene and alternative splicing

The type II procollagen gene has always been a souce of inspiration for me. Having fallen in love with DNA and RNA while a graduate student, my first significant contribution to science was the cloning of the type II collagen gene in 1980 and setting up the first ever DNA sequencing experiment at the University of Chicago (together with Dr. Elaine Fuchs, a newly arrived Assistant Professor) using the Maxim and Gilbert technique. There is nothing more scientifically exhilarating than reading DNA sequence and understanding its message! We cloned and sequenced type II collagen cDNA then isolated the gene and defined the intron/exon structure and sequence of the COOH-propeptide of both the chicken and human collagen genes. This data provided the first protein sequence of the type II collagen protein. We continued to analyze the human gene, now investigating the promoter for regulatory domains and the NH2-propeptide for sequence and structure. While sequencing the promoter and first few exons we made a remarkable discovery, the type II collagen gene contained an additional exon between the first exon and what was thought to be the second exon: this exon 2 was found to be alternative spliced and now represents the real commitment step in the conversion from a skeletal precursor cell (+exon 2) to a chondrocyte (-exon). Of the 50 papers we have published on the topic of the type II collagen gene structure and alternative splicing, three seminal papers are listed below.

a. Upholt, W. B. & **Sandell, L. J.** Exon/intron organization of the chicken type II procollagen gene: intron size distribution suggests a minimal intron size. Proceedings of the National Academy of Science 83: 2325-2329, **1986.**
b. **Sandell, L. J.,** Morris, N., Robbins, J. R. & Goldring, M. R. Alternatively spliced forms of type II collagen mRNA define distinct populations of cells during vertebral development: differential expression of the amino-propeptide. Journal of Cell Biology 114: 1307-1319, **1991**
c. McAlinden, A., Havlioglu, N., Liang, L., Davies, SD and **Sandell, L. J**. Alternative splicing of type II procollagen exon 2 is regulated by the combination of a weak 5' splice site and an adjacent intronic stem-loop cis element. Journal of Biological Chemistry 280:32700-32711, **2005**.

This work lead directly to the finding of IIA N-propeptide in serum and the development of an assay for protein in serum and for mRNA covered under the following patents. The antibody assay is now commercialized (Merck-Germany) and being used in clinical osteoarthritis studies. Recent evidence from the Foundation for NIH study on OA Biomarkers indicates that PIIANP is one of the four biomarkers that predict progression of OA and will be forwarded to the FDA for validation.

- "Assays for Cartilage Synthesis in Osteoarthritis Based on Detection of Type IIA mRNA". U.S. Patent #5,541,066. Issued: July 30, 1996
- "Assays for Cartilage Synthesis in Osteoarthritis Based on Detection of Type IIA Procollagen/Propeptide or Type IIA mRNA". U.S. Patent #5,541,066. Issued: July 14, 1998

2. CD-RAP: Discovery and use as a model for gene expression

I have always been interested in large scale screening techniques because they allow for the unbiased discovery of molecules that are not yet "candidates". Our first screen was with the technique of differential display of mRNA: our screen was for molecules responsive to retinoic acid in chondrocytes.

a. Xie, W-F., Zhang, X., Sakano, S., Lefebvre, V. & **Sandell, L. J.** Trans-activation of mouse cartilage-derived retinoic acid-sensitive protein by the transacting factor sox9. Journal of Bone and Mineral Research 14(5): 757-763, **1999**.
b. Imamura, T., Imamura, C., Iwamoto, Y., and **Sandell, L. J.** Transcriptional co-activator CBP/p300 increase chondrocyte Cd-rap gene expression by multiple mechanisms including sequestration of the repressor CCAAT/enhancer-binding protein. Journal Biological Chemistry 280:16625-16634, **2005**.
c. Davies, S.R., Li, J., Okazaki, K. & **Sandell, L. J**. Differential regulation of the cdrap gene within a conserved, multigenic housekeeping locus. Genomics 83(4): 667-78, **2004**.

d. Zhang Z, Bryan JL, DeLassus E, Chang LW, Liao W, **Sandell LJ**. CCAAT/enhancer-binding protein β and NF-κB mediate high level expression of chemokine genes CCL3 and CCL4 by human chondrocytes in response to IL-1β. J Biol Chem. **2010** Oct 22;285(43):33092-103.

3. **The type II collagen NH_2-propeptides: Pro-life and Cell Death**
Over the years, the function of the NH_2-propeptides, named type IIA (+exon 2) and type IIB (-exon 2) has intriqued us. Exon 2 (type IIA) encodes a von Willibrand Factor C domain that can bind to and sequester TGFB and BMPs in the ECM: this was one of the first growth factor binding regulatory proteins defined. We further characterized the function of the type IIB NH_2-propeptide and found that it can kill cells dependent on the integrin receptors α_vB_3 and α_vB_5. We will soon publish the definitive study demonstrating that type IIB NH_2-propeptide is anti-angiogenic. Thus, IIA is pro-life and IIB kills cells. This is why the alternative splicing is critical: the IIA splice form protects the cells it is synthesized by particularly during development (chondroprogenitors, embryonic heart, kidney, basement membrane and vitreous), but the IIB form synthesized by chondrocytes can protect the cells from invasion by tumor cells, osteoblasts and endothelial cells.

   a. Zhu, Y., Oganesian, A., Keene, D. R. & **Sandell, L. J.** Type IIA procollagen containing the cysteine-rich amino propeptide is deposited in the extracellular matrix of prechondrogenic tissue and binds to TGF – β1 and BMP-2. *Journal of Cell Biology* 144: 1069-1080, **1999**
   b. Wang,Z., Bryan, J., Franz, C., Havlioglu,N. and **Sandell, L.J.** Type IIB procollagen NH_2-Propeptide induces death of tumor cells via interaction with interaction with integrins α_vB_3 and α_vB_5. *Journal Biological Chemistry* Jul 285: 2006-20017. **2010**
   c. Hayashi, S., Wang, Z., Bryan, J., Kobayashi, C., Faccio, R., **Sandell, L.J.** The N-propeptide of type IIB collagen inhibits function and survival of osteoclasts, but not osteoblasts, via integrin-mediated signaling. *Bone*., 49(4):644-52. **2011**

4. **Genetic mouse models of osteoarthritis: analysis of a complex genetic disease.**
We hypothesized that people who could repair their cartilage were less susceptible to OA. Therefore we undertook a study of the genetics of cartilage repair. In our efforts to shift the paradigm in OA research, we undertook genetic studies from a population genetics point of view to reflect the heterogeneity in the human population. We worked with population geneticist, Dr. Jim Cheverud, who had developed recombinant inbred lines and an advanced intercross (F44) of Lg and Sm mice. Lg is a healer mouse (related to MRL) and Sm is a non-healer of ear tissue. We examined phenotypes for cartilage repair. We indeed found that cartilage repair was genetic and inversely proportional to the susceptibility to OA.

   a. Rai, MF., Hashimoto, S., Johnson, EE., Janiszak, KL., Fitzgerald, J, Heber-Katz E, Cheverud, JM., **Sandell, LJ**. Heritability of articular cartilage regeneration and its association with ear wound healing in mice. *Arthritis Rheum*. 64(7):2300-10. **2012.**
   b. Hashimoto, S., Rai, MF., Janiszak, KL., Cheverud, JM., **Sandell, LJ.** Cartilage and bone changes during development of post-traumatic osteoarthritis in selected LGXSM recombinant inbred mice. *Osteoarthritis Cartilage*. 20(6):562-71. **2012**.
   c. Rai MF, Schmidt EJ, Hashimoto S, Cheverud JM and **Sandell LJ.** Genetic Loci that Regulate Ectopic Calcification in Response to Knee Trauma in LG/J by SM/J Advanced Intercross Mice. Journal of Orthopaedic Research, Vol 33 (10):1412-1423. **2015.**

Complete List of Published Work in My Bibliography: **Note:** Dr. Sandell is the Co - PI of the P30 NIAMS grant and thus all publications from the members of the Musculoskeletal Research Center link to Dr. Sandells NCBI list. While we make every attempt to remove them for the purpose of the NIH Biosketch, recent ones may have been added since this grant was submitted. https://scholar.google.com/citations?user=Ch4H4x8AAAAJ&hl=en

D. RESEARCH SUPPORT

Ongoing Research Support

2009/05/11-2019/03/31
P30 AR057235-07, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
SANDELL, LINDA J (PI)
Core Center for Musculoskeletal Biology and Medicine

Role: PI

2015/04/01-2020/03/31
R01 AR066590-01, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
PATRA, DEBABRATA; SANDELL, LINDA J (M-PI)
The Dynamic Range of Site-1 Protease Functions in Skeletal Development
Role: Co-PI

Completed Research Support

2014/01/30-2015/12/31
FIDA FARMACEUTICI S.P.A.
SANDELL, LINDA J (PI)
Study of Early and Late Responses to Intra-articular
Role: PI

1998/03/01-2015/08/31
R01 AR045550-15, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
SANDELL, LINDA J (PI)
Function and Regulation of CD-RAP
Role: PI

2003/09/26-2013/08/31
R01 AR050847, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
SANDELL, LINDA J (PI)
Cis Regulatory Motifs in Adult Articular Chondroytes
Role: PI

1985/09/01-2013/08/31
R01 AR36994, National Institutes of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
SANDELL, LINDA J (PI)
Regulation of Gene Expression in Cartilage
Role: PI

2009/04/01-2011/03/31
SANDELL, LINDA J and CHEVERUD, JAMES
RC2 AR058978, National Institutes of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Grand Opportunity Grant
Genetics of Cartilage Repair and Osteoarthritis
Role: Co-PI

2014/05/01-2016/04/30
K99/R01 AR0664837-02, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Rai, M. Farooq (PI) Genetic and Molecular Insights into Cartilage Regeneration
Role: Mentor