BIOGRAPHICAL SKETCH

NAME: Zulma Gazit			
eRA COMMONS USERNAME: ZGAZIT			
POSITION TITLE: Associate Professor of Surgery			
INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Buenos Aires, Argentina	M.Sc.	1977	Biochemistry
Hebrew University of Jerusalem, Israel	Ph.D	1994	Immunology
University of California in San Francisco, San Francisco, USA	Post Doctorate	1992	Immunology

A. Personal statement

I entered the field of research on adult mesenchymal stem cells (MSCs) in the year 2000, after being focused in immunology. Since both systems share a common niche, that is the bone marrow, the move from immunology to mesenchymal stem cells and skeletal tissue regeneration was a natural one. My studies have shown that MSCs were able to generate and regenerate bone when genetically modified to overexpress an osteogenic gene. I viewed the usual methods to isolate MSCs as ineffective to be applied in clinical setting, so I developed the methodology for immunoisolated, noncultured MSCs for in vivo implantation and reported that human MSCs can be immunoisolated and induced to differentiate into bone tissue without prior need of expansion. Later on my focus moved to MSCs residing in another tissues such as adipose tissue and the intervertebral disc. In the paper "Evidence for Skeletal Progenitor Cells in the Degenerate Human Intervertebral Disc" (*Spine, 2007*) prepared in collaboration with Dr I. Shapiro, Jefferson University, PA, it was clearly shown that stem cells do exist in the IVD, even in its degenerated state. As Principal Investigator in a NIHR03 grant, "Stem Cells from the Intervertebral Disc: Do They Vary in Degeneration?", I investigated the contribution of stem cells (SC) to IVD degeneration. The proposed project is still relevant from both fundamental biological and clinical perspectives. The published findings gave a first step in understanding why resident SCs do not reverse the degenerative process within the disc (*The Spine Journal, 2013*). Just this month our paper entitled "Matrix Stiffness Determines the Fate of Nucleus Pulposus-Derived Stem Cells" was accepted for publication in *Biomaterials*. With the discovery of induced pluripotent stem cells –iPSC- there has been an exponential development and advanced technology with enormous potential to progress medical therapy by personalizing regenerative medicine. Apart from the prospects of using iPSCs in regenerative therapy, I blend the paths between IVD-derived cells and iPSC to generate early developed iPSC-derived notochordal and nucleus pulposus cells. The goal is to use these cells to rescue damaged tissues, namely degenerate disc. My work has been reported in leading journals including: *Stem Cells, Gene Therapy, Biomaterials, Tissue Engineering, Journal of Bone and Mineral Research, and Molecular Therapy*. In addition, I have presented both invited and competitive lectures at numerous national and international meetings such as the Orthopedic Research Society, American Society of Cell and Gene Therapy, Tissue Engineering and Regenerative Medicine International Society, and the International Society of Stem Cell Research. Over the last four years I conducted a project supported by the National Institutes of Health, where structural allografts are used for cranioplasty together with intermittent PTH administration; a significant bone repair and graft integration occurred more efficiently than in allografts without PTH. No doubt that these findings may potentially aid in the development of an attractive bone graft, which is readily available, for use in craniofacial reconstruction. The study was published in the Nov. 8, 2013 issue of the journal *Molecular Pharmaceutics*. Yet, to achieve an effective biointegration of an external construct stands as unsuccessful, mostly due to fibrosis at the graft-host suture. Once we deal with the primary problem, inflammation and mast cells in the interface, we plan to use the 3D printed custom constructs that in the future can be further enhanced by impregnating angiogenic (VEGF) and/or osteogenic (BMP) factors, and even osteogenic cells into the scaffold during manufacturing in a manner that cannot be done with allografts. My work has been reported in leading journals including: Stem Cells, Gene Therapy, Biomaterials, Tissue Engineering, Journal of Bone and Mineral Research, and Molecular Therapy. In addition, I have presented both invited and competitive lectures at numerous national and international meetings such as the Orthopedic Research Society, American Society of Cell and Gene Therapy,

Tissue Engineering and Regenerative Medicine International Society, and the International Society of Stem Cell Research.

B. Positions and Honors

Positions and Employment

2006-present Co-Director, Skeletal Regeneration and Stem Cell Therapy Program, Department of Surgery and Regenerative Medicine Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

2000-present Senior Scientist, Stem Cell Biology and Immunology, Faculty of Dental Medicine, Hebrew University, Jerusalem, Israel.

2003-2006 Visiting Senior Scientist, Department of Neurosurgery, Faculty of Medicine, University of Virginia, Charlottesville, VA, USA.

1983-1987 Young Scientist, The Lautenberg Center for General and Tumor Immunology, Faculty of Medicine, Hebrew University, Jerusalem, Israel.

Other Experience and Professional Memberships

Ad Hoc Reviewer for the following Journals and Associations:
Stem Cells
Gene Therapy
Biomaterials
Tissue Engineering
Journal of Orthopedic Research
Arthritis Research and Therapy
The Musculoskeletal Transplant Foundation (MTF), Grant reviewer
The Israeli Stem Cell Society, Grant Reviewer
Peer Reviewed Medical Research Program (PRMRP), Ad Hoc Reviewer

Professional Activities:
2005-2010 Member, Steering Committee of the Israeli Consortium *Bereshith* ("Genesis") for Cell Therapy.
2005-2011 Member, Founder, Steering Committee of the Israel Stem Cell Society.
2011-2013 Treasurer, the Israel Stem Cell Society

C. Contribution to Science

Immunoisolation of Mesenchymal Stem Cells: Mesenchymal stem cells constitute a unique population of adult stem cells that holds great promise for various tissue-engineering and regenerative medicine applications. These cells can readily be isolated from various sites in the human body, especially from bone marrow and adipose tissues. Established protocols exist for the induction of specific differentiation patterns of MSCs into different committed cells, most notably osteoblasts, chondrocytes, and adipocytes. The conventional method of MSC isolation using plastic adherence has proved to be costly and may reduce the stem quality of cells in vivo, making them fail to meet the desired goal. It has been reported that cultured human (h)MSCs may undergo spontaneous transformation as a consequence of their in vitro expansion. In few studies has the use of noncultured freshly isolated hMSCs been described. **Therefore, an alternative method involving the immediate use of immunoisolated, noncultured MSCs for in vivo implantation was viewed by me as an unmet need in the field of regenerative medicine.** In relation to clinical settings, the aim of immunoisolation is to enrich implants, such as bone substitutes, with MSCs that provide osteogenic progenitors. **"Osteogenic differentiation of noncultured immunoisolated bone marrow–derived CD105+ cells"** ***(Stem Cells 2006)*** was the first report using this approach became a highly relevant, high cited paper because of its importance to clinical applications as well as basic approaches. The immediate outcome of this project was a Phase I clinical trial in Hadassah Hospital, Jerusalem and results were recently published in **Stem Cell-based Therapy for Prevention of Delayed Fracture Union: A Randomized and Prospective Preliminary Study (*Molecular Therapy 2013*).**

1. Liebergall M, Schroeder J, Mosheiff R, **Gazit Z,** Yoram Z, Rasooly L, Daskal A, Khoury A, Weil Y, Beyth S. Stem cell-based therapy for prevention of delayed fracture union: a randomized and prospective preliminary study. Mol Ther. 2013 Aug;21(8):1631-8.
2. **Gazit Z**, Pelled G, Sheyn D, Kimelman N, Gazit D. "Mesenchymal Stem Cells", in Principles of Regenerative Medicine, 2nd edition, Atala A, Lanza R, Thomson JA, and Nerem RM. Eds. Elsevier Inc. 2011.
3. Aslan H, Zilberman Y, Kandel L, Liebergall M, Oskouian RJ, Gazit D, **Gazit Z.** Osteogenic differentiation of noncultured immunoisolated bone marrow-derived CD105+ cells. Stem Cells. 2006 Jul;24(7):1728-37.

4. Steinhardt Y, Aslan H, Regev E, Zilberman Y, Kallai I, Gazit D, **Gazit Z.** Maxillofacial-derived stem cells regenerate critical mandibular bone defect. Tissue Eng Part A. 2008 Nov;14(11):1763-73.

Nonviral Gene Delivery: So far it has been demonstrated that the use of genetically modified MSCs overexpressing various therapeutic transgenes is a powerful tool in the induction of differentiation of cells and in the promotion of tissue regeneration in vivo. Nonviral approaches to gene delivery hold great promise for the development of an efficient and safe cell-mediated gene therapy for orthopedic and other clinical applications. Bone regeneration requires only a short duration of transgene expression. Therefore, the transient expression achieved by nonviral gene delivery is highly advantageous, compared with long-term transgene expression following the use of genome-integrating viruses such as retroviruses and adeno-associated virus. **I see myself as a leading pioneer in the use of the nucleofection method to deliver the osteogenic human morphogenetic protein genes (*hBMPs) 2, 6* and *9* to hMSCs for the purpose of forming bone tissue.** We achieved the purpose to elucidate the interaction between bone marrow-derived and adipose tissue-derived MSCs with BMP-2 or BMP-6 genes to be applied in bone regeneration, and very clearly we showed that in **"BMP-6 is more efficient in bone formation than BMP-2 when overexpressed in mesenchymal stem cells."** ***(Gene Therapy, 2013).***

A very attractive project dealing with a novel ultrasound-based gene delivery method that resulted in bone tissue formation in vivo was published as "**Ultrasound-based nonviral gene delivery induces bone formation in vivo"** ***(Gene Ther. 2007)*** Direct gene delivery, in general, and ultrasound-based gene delivery, in particular, have gained a great deal of interest in the last few years due to their relative safety and ease of administration. This work demonstrated greater value than other direct gene delivery modalities and add to the quality of tissue engineering and clinical orthopedics for human applications, being these days the basis for an Early Translational CIRM Award project from our lab: CIRM TR4-06713 Gene Targeting to Endogenous Stem Cells for Segmental Bone Fracture Healing, (2013 –2016). Purpose: To achieve a development candidate of ultrasound-mediated gene targeting to endogenous MSCs for bone repair.

1. Aslan H, Zilberman Y, Arbeli V, Sheyn D, Matan Y, Liebergall M, Li JZ, Helm GA, Gazit D, **Gazit Z**. Nucleofection-based ex vivo nonviral gene delivery to human stem cells as a platform for tissue regeneration. Tissue Eng. 2006 Apr;12(4):877-89
2. Sheyn D, Pelled G, Zilberman Y, Talasazan F, Frank JM, Gazit D, **Gazit Z**. Nonvirally engineered porcine adipose tissue-derived stem cells: use in posterior spinal fusion. Stem Cells. 2008 Apr;26(4):1056-64.
3. Sheyn D, Kimelman-Bleich N, Pelled G, Zilberman Y, Gazit D, **Gazit Z**. Ultrasound-based nonviral gene delivery induces bone formation in vivo. Gene Ther. 2008 Feb;15(4):257-66.
4. Mizrahi O, Sheyn D, Tawackoli W, Kallai I, Oh A, Su S, Da X, Zarrini P, Cook-Wiens G, Gazit D, **Gazit Z**. BMP-6 is more efficient in bone formation than BMP-2 when overexpressed in mesenchymal stem cells. Gene Ther. 2013 Apr;20(4):370-7

Bone Allograft and teriparatide (PTH) to heal calvarial bone defects –Currently, one of the preferred alternatives is to use bone grafts received from tissue banks, but they often don't join with the bone they're supposed to fix. Parathyroid hormone (PTH), a drug approved by the U.S. Food and Drug Administration to treat osteoporosis, helps repair fractures in long bones. We reported progress toward a new hormone therapy that could improve the outcomes of these surgeries. Our studies, which are being conducted on mice, appeared in the ACS journal Molecular Pharmaceutics, "**PTH promotes allograft integration in a calvarial bone defect"**. Daily short-term PTH treatment improved bone formation around the grafts and prevented scar tissue, which can interfere with graft integration, from forming. We believe that these findings will aid in the development of an attractive bone graft, which is readily available, for use in craniofacial reconstruction.

1. Sheyn D, Cohn Yakubovich D, Kallai I, Su S, Da X, Pelled G, Tawackoli W, Cook-Weins G, Schwarz EM, Gazit D, **Gazit Z**. PTH promotes allograft integration in a calvarial bone defect. Mol Pharm. 2013 Dec 2;10(12):4462-71
2. ACS News Service Weekly PressPac: November 20, 2013. Hormone therapy could enhance the therapeutic effect of head and facial bone grafts.
3. Ben Arav A, Pelled G, Zilberman Y, Kimelman-Bleich N, **Gazit Z,** Schwarz EM, Gazit D. Adeno-associated virus-coated allografts: a novel approach for cranioplasty. J Tissue Eng Regen Med. 2012 Nov;6(10):e43-50.

Intervertebral Disc Degeneration - Resident Stem Cells in the Nucleus Pulposus: To date the effect of IVD degeneration on progenitors cells residing in the NP is not fully understood. In **"Nucleus pulposus degeneration alters properties of resident progenitor cells"** ***(Spine J. 2013)*** we investigated the functionality of NP-derived cells from porcine degenerated discs and compared it to the functionality of cells isolated from healthy porcine discs obtained from the same animal. **This work was supported by the NIH:** R03 AR057143-01 "Stem cells from the

intervertebral disc: do they vary in degeneration?" - Purpose: The proposed study aimed to investigate stem cells residing in the nucleus pulposus. My role: PI.
Having demonstrated that cultures of NP-derived SCs from degenerate discs differ in their proliferation and differentiation capacities when compared to cells from healthy discs, we proposed that extracellular matrix stiffness and changes in the elasticity of the degenerated disc matrix are associated with the impaired function of resident NP-SCs, which probably contributes to the onset of the IVD degeneration process. The obtained results highlight the effect of matrix stiffness on the fate of NP-SCs in "**Matrix Stiffness Determines the Fate of Nucleus Pulposus–Derived Stem Cells"** ***(Biomaterials 2015)*** This research may pave the way for a better understanding of the complex cross-talk of cells and their matrix during disc degeneration, as well as present novel therapeutic strategies for IVD regeneration.

1. Helm GA, **Gazit Z**. Future uses of mesenchymal stem cells in spine surgery. Neurosurg Focus. 2005 Dec 15;19(6):E13. Review.
2. Risbud MV, Guttapalli A, Tsai TT, Lee JY, Danielson KG, Vaccaro AR, Albert TJ, **Gazit Z**, Gazit D, Shapiro IM. Evidence for skeletal progenitor cells in the degenerate human intervertebral disc.Spine (Phila Pa 1976). 2007 Nov 1;32(23):2537-44.
3. **Gazit Z**, Pelled G, Sheyn D, Kimelman N, Gazit D. "Mesenchymal Stem Cells", in Principles of Regenerative Medicine, 2nd edition, Atala A, Lanza R, Thomson JA, and Nerem RM. Eds. Elsevier Inc. 2011.
4. Mizrahi O, Sheyn D, Tawackoli W, Ben-David S, Su S, Li N, Oh A, Bae H, Gazit D, **Gazit Z**. Nucleus pulposus degeneration alters properties of resident progenitor cells. Spine J. 2013 Jul;13(7):803-14.
5. Navaro Y, Bleich-Kimelman N, Hazanov L, Mironi-Harpaz I, Shachaf Y, Garty S, Smith Y, Pelled G, Gazit D, Seliktar D, **Gazit Z**. Matrix stiffness determines the fate of nucleus pulposus-derived stem cells. Biomaterials. 2015 May;49:68-76.

Complete List of Published Work in:

MyBibliography:http://www.ncbi.nlm.nih.gov/sites/myncbi/1naunvPS7jyAo/bibliography/44954377/public/?sort=date&direction=ascending.

Google Scholar: https://scholar.google.co.il/citations?user=4X1wEGMAAAAJ&hl=en

D. **Research Support**.

Ongoing Research Support

1. CIRM TR4-06713 Gene Targeting to Endogenous Stem Cells for Segmental Bone Fracture Healing
12/2013 – 12/2016 Purpose: To achieve a development candidate of ultrasound-mediated gene targeting to endogenous MSCs for bone repair. Role: Co-I
2. Cedars-Sinai Translational Research Pipeline: "A Combined Treatment of Gene Modified Stem Cells and Oxygenated Scaffolds for Scaphoid Nonunion with Avascular Necrosis" 06/2013 – 12/2015
Purpose: Tackling the important clinical issue of avascular necrosis. The overall objectives will focus on scaphoid nonunion to develop a tractable, clinically relevant model to augment the limited blood supply. Role: PI

Completed Research Support:

CIRM TR2-01780 "Systemic Adult Stem Cell Therapy for Osteoporosis-Related Vertebral Compression Fractures". 03/2011- 02/2014 Purpose: The goals of the project are to develop a stem cell-based therapy for osteoporotic vertebral fractures. Our hypothesis is that that PTH will induce MSC homing to the bone defects leading to accelerated bone repair. Role: Co-investigator.

NIH R01DE19902 "PTH Effects on Craniofacial Allografting" (PI – D. Gazit). 6/1/09- 5/31/14 Purpose: The goal of the proposal is to define the effects of PTH on bone healing using allografts with specific emphasis on scar tissue formation and inflammation. Role: Co-investigator.

NIH R03 AR057143-01 "Stem cells from the intervertebral disc: do they vary in degeneration?" 07/2009-06/2013 - Purpose: The proposed study aimed to investigate stem cells residing in the nucleus pulposus. The hypothesis was that stem cells residing in the degenerated nucleus pulposus demonstrate a change in their number and/or differentiation profile compared to SC in healthy discs. Role: PI