BIOGRAPHICAL SKETCH

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NAME: Dmitriy Sheyn

eRA COMMONS USER NAME (credential, e.g., agency login): SHEYND3

POSITION TITLE: Assistant 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	Completion Date MM/YYYY	FIELD OF STUDY
Hebrew University of Jerusalem, Faculty of Medicine	BSc	06/2004	Basic Medical Sciences
Hebrew University of Jerusalem, Faculty of Dental Medicine	MSc	10/2005	Skeletal Tissue Engineering
Hebrew University of Jerusalem, Faculty of Dental Medicine	PhD	10/2010	Skeletal Tissue Engineering
Cedars-Sinai Medical Centre, Department of Surgery, Regenerative Medicine Institute	Postdoc	10/2013	Stem Cell-Based Skeletal Regeneration

A. Personal Statement

This field of gene-and-stem cell therapy holds a great therapeutic potential. I have developed an efficient and easily reproducible method to modify stem cells and to regenerate bone defects and generate new bone tissue for spinal fusion. The cell therapy approach was tested and found biomechanically comparable to the native bone. This is of enormous importance since the current clinical practice mostly involves artificial materials that are extremely far from the native tissues by their biomechanical properties, which often causes rejection and failure. During my postdoc I studied the effect of PTH on bone repair and stem cell recruitment to the injury site in osteoporotic and healthy animal models. I have developed a protocol to differentiate induced pluripotent stem cells (iPSCs) into a new stem cell entity, characterized it and used for segmental bone defects repair. Currently I'm developing new applications for adult and pluripotent stem cells in the field of skeletal tissue regeneration, particularly focusing on the soft tissues of knee and intervertebral disc. Sports medicine is of particular interest of mine, since the soft tissue injuries have very limited solutions these days. I'm applying the knowledge and expertise I gained during the years in the genetically modified stem cell research, translational large animal models and imaging to bring new remedies to the soft tissue injuries. This project specifically is fascinating, because we will not try to repair the damaged cartilage, which many groups attempt to do. We will try to prevent the degeneration, since it has a clear starting point (unlike IVD degeneration), the ACL injury and reconstruction. We have collaborated with Dr. Kremen before and we have the full support of the Department of Orthopedics and the Regenerative Medicine Institute at Cedars-Sinai and The Department of Orthopedic surgery at UCLA to conduct the proposed research project. Our facilities in Cedars Sinai medical center include state-of-the-art imaging core, animal surgery and maintenance facilities and tissue engineering equipment and capabilities that are required to execute this project. Additionally, a stem cell GMP facility is being established in our institute, which will allow to advance the findings of this project to the next step of clinical grade cell product for clinical studies. Overall, we have assembled a team of investigators from Cedars and UCLA that will be synergistic for the current R21 proposal and will be able to push this technology forward towards clinical application and mechanistic studies that will function as foundation for more in depth studies in a R01 funding mechanism.

B. Positions and Honors

Positions and Employment

11/2013 – 11/2015	Project Scientist in Skeletal program of Regenerative Medicine Institute, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA.
11/2015 – 12/2018	Research Scientist I in BOG Regenerative Medicine Institute, Departments of Orthopedics and Surgery, Cedars-Sinai Medical Center, Los Angeles, CA.
06/2016 – present	Assistant Professor in BOG Regenerative Medicine Institute, Department of Orthopedics, Department of Surgery, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA.
12/2018 – present	Research Scientist II in BOG Regenerative Medicine Institute, Department of Orthopedics, Department of Surgery, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA.

Other Experience and Professional Memberships

- Tissue Engineering and Regenerative Medicine (TERMIS) – member since 2010
- North American Spine Society (NASS)- member since 2011
- International Society for Stem Cell Research (ISSCR)- member since 2012
- Orthopaedic Research Society (ORS) – Member since 2011, Member of the ORS membership committee and the ORS ambassador in South California region since 2016

Manuscript reviewer:

Molecular Biotechnology, Journal of Biomedical Materials Research: Part A, Tissue Engineering, PLOS One, BMC Musculoskeletal Disorders, Journal of Biological Engineering, Journal of Tissue Engineering and Regenerative Medicine, Biochimi, Biomaterials, Journal of Materials Science: Materials in Medicine.

Honors

2007 – 2010	Rector's Fellowship for outstanding doctoral students
2007 – 2010	Levy Eshkol doctoral fellowship, provided by Israeli Ministry of Science
2007	The Kaye Innovation Award at Hebrew University of Jerusalem
2008	Rusk Foundation Travel Award for excellent graduate students
2008	Best Basic Science Paper – 16th Ann Scientific Mtg of the Int'l Spine Intervention Society
2010 – 2012	Regenerative Medicine Institute fellowship for postdoctoral researcher
2013	Best Oral Presentation Award at Regenerative Medicine Institute Annual Retreat
2014	Finalist, New Investigator Research Award (NIRA); ORS annual meeting 2014
2017	Finalist, New Investigator Research Award (NIRA); ORS annual meeting 2017

C. Contribution to Science

1) **Genetically engineered stem cells are a tool for tissue engineering and regenerative medicine**, albeit a tool whose development is fraught with difficulties. Gene-and-cell therapy offers solutions to severe problems faced by modern medicine, but several impediments obstruct the path of such treatments as they move from the laboratory toward the clinical setting (a). One of the main focuses of my research was to develop gene-and-stem cell therapy for bone tissue related disorders. My colleagues and me have developed an efficient and easily reproducible method to modify stem cells to regenerate bone fractures and generate new bone tissue and repair vertebral compression fractures. Our studies in this area have demonstrated that the adipose-derived stem cells overexpressing osteogenic factors can restore significant defects and injuries in the vertebral body otherwise incurable (b-c). Our data provide the platform for new stem cell-based approaches for treating vertebral fractures especially in osteoporotic patients (d). Mesenchymal stem cells (MSCs) are currently the most established cells for skeletal tissue engineering and regeneration; however, their availability and capability of self-renewal are limited. Recent discoveries of somatic cell reprogramming may be used to overcome these challenges. In just accepted study we developed a new method to differentiate MSCs from induced pluripotent stem cells (iPSCs) and showed that those cells can generate bone tissue in vivo and regenerate critically sized bone defect (d).

a) **Sheyn D**, Pelled G, Zilberman Y, Talasazan F, Frank JM, Gazit D and Gazit Z, Nonvirally Engineered Porcine Adipose Tissue–derived Stem Cells: Use in Posterior Spinal Fusion, *Stem Cells,* 2008; Apr;26(4):1056-64

b) **Sheyn D,** Kallai I, Tawackoli W, Cohn Yakubovich D, Oh A, Su S, Da X, Lavi A, Kimelman-Bleich N, Zilberman Y, Li N, Bae H, Gazit Z, Pelled G, Gazit D. Gene-Modified Adult Stem Cells Regenerate Vertebral Bone Defect in a Rat Model. *Mol Pharm.* 2011 Oct 3;8(5):1592-601.
c) Pelled G#, **Sheyn D#(equal contributor)**, Tawackoli W#, Jun DS, Koh Y, Su S, Cohn Yakubovich D, Kallai I, Antebi B, Da X, Gazit Z, Bae H, Gazit D. BMP6-Engineered MSCs Induce Vertebral Bone Repair in a Pig Model: A Pilot Study. *Stem Cells Int*. 2016;2016:6530624. doi: 10.1155/2016/6530624. Epub 2015 Dec 7.
d) **Sheyn D,** Ben-David S, Shapiro G, De Mel S, Bez M, Ornelas L, Sahabian A, Sareen D, Da X, Pelled G, Tawackoli W, Liu Z, Gazit D, Gazit Z, "Human iPSCs differentiate into functional MSCs and repair bone defect" *Stem Cells Translational Medicine*, 2016 Nov;5(11):1447-1460. doi: 10.5966/sctm.2015-0311. Epub 2016 Jul 11.

2) **Novel non-viral gene delivery methods for bone formation and regeneration.** To enhance the efficiency of non-viral gene delivery, methods have been developed that rely on a short pulse of energy to optimize gene delivery. These methods induce the formation of transient nano-sized pores in the membranes of cells, enabling the uptake of DNA, which leads to cell transfection. After developing a method for ex vivo electroporation-based gene delivery method (a), my colleagues and I developed a novel gene delivery method for bone formation and regeneration and currently prospectively validating data that may contradict current thinking about the direct gene delivery strategy (b, c, d). In this regard, it is truly astounding that ultrasound-based gene delivery system that resulted in in vivo bone formation de novo (b). This method is specifically appealing for long bone superficial non-union fractures. The study involves targeting endogenous stem cells and induction of their differentiation. And in recognition of the importance of this discovery, the California Institute of Regenerative Medicine recently funded a further study with the prestigious Early Translational Award III to develop a preclinical model for such treatment for non-union fractures in long bones. The outcome of this study will generate a simple, affordable and safe solution for non-union fractures.

a) 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 Engineering.* 2006;12(4):877-89.
b) **Sheyn D,** Kimelman-Bliech N, Pelled G, Zilberman Y, Gazit D and Gazit Z, Ultrasound-based Nonviral Gene Delivery Induces Bone Formation In Vivo, *Gene Therapy,* 2008, Feb;15(4):257-66
c) Bez M, Kremen TJ, Tawackoli W, Avalos P, **Sheyn D**, Shapiro G, Giaconi JC, Ben David S, Snedeker JG, Gazit Z, Ferrara KW, Gazit D, Pelled G. Ultrasound-Mediated Gene Delivery Enhances Tendon Allograft Integration in Mini-Pig Ligament Reconstruction. Mol Ther. 2018 Jul 5;26(7):1746-1755. doi: 10.1016/j.ymthe.2018.04.020. Epub 2018 Apr 26. PubMed PMID: 29784586
d) Bez M, **Sheyn D**, Tawackoli W, Avalos P, Shapiro G, Giaconi JC, Da X, David SB, Gavrity J, Awad HA, Bae HW, Ley EJ, Kremen TJ, Gazit Z, Ferrara KW, Pelled G, Gazit D. In situ bone tissue engineering via ultrasound-mediated gene delivery to endogenous progenitor cells in mini-pigs. *Sci Transl Med*. 2017 May 17;9(390). pii: eaal3128. doi: 10.1126/scitranslmed.aal3128.

3) **Regeneration of tendons and ligaments injuries** Soft tissue healing and regeneration is an important unmet need in the treatment of musculoskeletal injuries. Strategies that avoid ex vivo manipulation of cells streamline this process. In collaboration with Dr. Kremen and Dr. Gazit we have successfully developed a large animal model of ligament-to-bone healing and a we have reported enhanced ACL graft incorporation in mini-pigs using ultrasound-mediated direct gene delivery (a). Additionally, our group investigates novel, yet clinically applicable, imaging strategies for monitoring the viability, biodistribution and proliferation of genetically engineered stem cells in a context of tendon defect regeneration (b).

a) Kremen TJ, Bez M, **Sheyn D**, Ben-David S, Da X, Tawackoli W, Wagner S, Gazit D, Pelled G. In Vivo Imaging of Exogenous Progenitor Cells in Tendon Regeneration via Superparamagnetic Iron Oxide Particles. Am J Sports Med. 2019 Jul 23;:363546519861080. doi: 10.1177/0363546519861080. [Epub ahead of print] PubMed PMID: 31336056.
b) Bez M, Kremen TJ, Tawackoli W, Avalos P, **Sheyn D**, Shapiro G, Giaconi JC, Ben David S, Snedeker JG, Gazit Z, Ferrara KW, Gazit D, Pelled G. Ultrasound-Mediated Gene Delivery Enhances Tendon Allograft Integration in Mini-Pig Ligament Reconstruction. Mol Ther. 2018 Jul 5;26(7):1746-1755. doi: 10.1016/j.ymthe.2018.04.020. Epub 2018 Apr 26. PubMed PMID: 29784586; PubMed Central PMCID: PMC6035740.

4) **Resident Stem Cells in the Nucleus Pulposus**: Degenerative intervertebral disc (IVD) disease and associated chronic lower back pain constitute a major health problem with estimated costs in the U.S. of up to

$50 billion yearly. Despite decades of research, no fundamental multidisciplinary understanding of the mechanism(s) of IVD degeneration has surfaced, and consequently, clinical therapies are still in the earliest stages of development. This debilitating disease is caused by cell-mediated functional tissue degradation in response to progressive structural failure. Degenerative changes are mediated by disturbances in the function of cells residing in the disc. The disc as organ possesses a minimal capability for intrinsic regeneration probably due to a malfunction in stem cells and early progenitors, repair cells, residing in the NP (a,b). 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 (c). This research may pave the way for a better understanding of the complex process of disc degeneration, as well as present novel therapeutic strategies for IVD regeneration. Developing novel imaging techniques for the IVD has enormous impact on IVD research and clinical protocols. Recently we developed a new MRI-based method to capture degeneration process of the disc (d).

a) Mizrahi O,# **Sheyn D, #(equal contributor),** 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.
b) Zhou Z, Bez M, Tawackoli W, Giaconi J, **Sheyn D,** Pelled G, Gazit D, Li D. Quantitative Chemical Exchange Saturation Transfer (qCEST) MRI of Intervertebral Disc in a Porcine Model, Magnetic Resonance in Medicine 2016 Dec;76(6):1677-1683. doi: 10.1002/mrm.26457
c) Bez M, Zhou Z, **Sheyn D**, Tawackoli W, Giaconi JC, Shapiro G, Ben David S, Gazit Z, Pelled G, Li D, Gazit D. Molecular pain markers correlate with pH-sensitive MRI signal in a pig model of disc degeneration. Sci Rep.2018 Nov 26;8(1):17363. doi: 10.1038/s41598-018-34582-6. PubMed PMID: 30478330; PubMed Central PMCID: PMC6255799

5) **Parathyroid hormone can facilitate regeneration of bone defects.** Osteoporosis affects more than 200 million people worldwide leading to more than 2 million fractures in the US alone. Unfortunately, surgical treatment is limited in patients with low bone mass. Parathyroid hormone (PTH) was shown to induce fracture repair in animals by activating mesenchymal stem cells (MSCs). However, it would be less effective in patients with fewer and/or dysfunctional MSCs due to aging and comorbidities. Parathyroid hormone (PTH) is approved for use by the FDA as an anabolic agent in the treatment of severe osteoporosis. Initial human studies with teriparatide have demonstrated its capacity to increase cancellous bone volume and connectivity as well as increase cortical thickness. Our study has shown that vertebral defects created in osteoporotic rats and in healthy pigs can be efficiently repaired following combined systemic administration of MSCs and PTH therapy (a). This contrasts with the results in animals that received either treatment alone or no treatment. Moreover, the results support the hypothesis that administration of PTH enhanced hMSC migration to vertebral bone defects in osteoporotic rats. In other study we have tested the mechanism of PTH therapy in enhancing allograft integration in craniofacial defect (b, c). Bone grafts, which are used to treat head injuries and birth defects, still pose major medical challenges. Surgeons perform nearly 100,000 head and facial bone-grafting procedures every year to treat bone loss from disease, birth defects or traumatic injuries. Currently, one of the preferred alternatives is to use bone grafts received from tissue banks, but they often don't integrate with the host bone tissue and fail. We reported progress toward a new hormone therapy that could improve the outcomes of these surgeries. Our studies (b, c, d), which were conducted on mice, showed that 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. The next step will be to enhance the revitalization of the allograft using specialized stem cells that have the potential to regenerate the cranial bone in more efficient way than MSCs that were isolated from long bones.

a) **Sheyn, D.,** Shapiro, G., Tawackoli, W., Jun, D.S., Koh, Y., Su, S., Da, X., Ben-David, S., Bez, M., Yalon, E., Antebi, B., Avalos, P., Stern, T., Zelzer, E., Schwarz, E.M., Gazit, Z., Pelled, G., Bae, H.M., Gazit, D., "PTH induces systemically administered mesenchymal stem cells to home to and regenerate osteoporotic spine injuries" *Molecular Therapy* (2015)
b) **Sheyn, D**., Cohn-Yakubovich, D., Kallai, K., Su, S., Pelled, G., Tawackoli, W., Gazit, D., Gazit, Z., "PTH promotes allograft integration in a calvarial bone defect, *Mol. Pharm,* Dec 2;10(12):4462-71 (2013)
c) Cohn Yakubovich D., Eliav U., Yalon E., Schary Y., **Sheyn D**., Cook-Wiens G., Sun S., McKanna C.E., Lev S, Binshtok A.M., Pelled G., Navon G., Gazit D., Gazit Z. "PTH attenuates scarring around murine cranial

bone allograft via modulation of angiogenesis" *Bone*, 2017 Jan 21;97:192-200. doi: 10.1016/j.bone.2017.01.020

d) Cohn Yakubovich D, **Sheyn D,** Bez M, Schary Y, Yalon E, Sirhan A, Amira M, Yaya A, De Mel S, Da X, Ben-David S, Tawackoli W, Ley EJ, Gazit D, Gazit Z, Pelled G. Systemic administration of mesenchymal stem cells combined with parathyroid hormone therapy synergistically regenerates multiple rib fractures. Stem Cell Res Ther. 2017 Mar 9;8(1):51. doi: 10.1186/s13287-017-0502-9.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1BULvGNqCBL/bibliography/41037283/public/?sort=date&direction=ascending

Books chapters:

1. **Sheyn D**, Pelled G, Gazit D. "Nanotechnologies in Adult Stem Cell Research", in Nanotechnology in Biology and Medicine: Methods, Devices, and Applications, Vo-Dinh T. Ed. 2007, CRC Press LLC.
2. Gazit Z, Pelled G, **Sheyn D**, Kimelman-Bleich N, Gazit D. Mesenchymal stem cells. Chapter 26 in "Regenerative Medicine and Tissue Engineering" textbook, Second edition, 2010.
3. Kimelman N, Kallai I, **Sheyn D**, Tawackoli W, Gazit Z, Pelled G, Gazit D. Real-time bioluminescence functional imaging for monitoring tissue formation and regeneration. *Methods Mol Biol*. 2013;1048:181-93. doi: 10.1007/978-1-62703-556-9_14.
4. Glaeser JD, Saitta B, **Sheyn D**, Bae HW. Musculoskeletal Stem Cells. Chapter 12 in "Regenerative Medicine - from Protocol to Patient", pp.315-343. doi: 10.1007/978-3-319-27610-6_12
5. Gazit Z. Pelled G. **Sheyn D.** Cohn-Yukubovich D. and Gazit D. Mesenchymal stem cells. Chapter in "Regenerative Medicine and Tissue Engineering" textbook, Third edition, (2017)

Ongoing Research Support

CIRM- DISC1-10643 Sheyn (PI). 03/2018 - 12/2019
California Institute of Regenerative Medicine
"IVD rejuvenation using iPSC-derived notochordal cells"
Purpose: To identify a new therapeutic agent for disc regeneration using novel pluripotent stem cells and injectable beads that support differentiation and provide biomechanical strength.

NIH/NIAMS 1K01AR071512-01A1 Sheyn (PI) 06/2018-04//2023
"Induced pluripotent stem cell therapy for degenerated IVD"
Purpose: Career development award

AOSSM Chahla, MD (PI) 09/2018-08/2020
"Revisiting the Vascularity and Stem Cell Population of the Meniscal Avascular Zone Using 3D Imaging Technique"
Role: Co-PI

Completed Research Support:

OREF Resident Clinician Scientist Training Grant Ju (PI) 07/2018 – 06/2019
"Identifying and mitigating the effects of diabetes on disc degeneration"
Role: Mentor and Co-I

MTF foundation: Young Investigator Award Sheyn (PI) 07/01/17-06/31/18
"Neural crest cells efficiently revitalize cranial allografts"
Purpose: to supplement structural allograft with neural crest stem cells to enhance revitalization