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TEL AVIV UNIVERSITY אוניברסיטת תל אביב

Zimin Institute for Engineering Solutions Advancing Better Lives

Title: Bioengineered three-dimensional design to promote neuronal regeneration

Principal Investigator: Dekel Rosenfeld, PhD

Senior Lecturer
Biomedical Engineering, Faculty of Engineering
Tel Aviv University

Scope of Research: Bioconvergence (and Bioengineering)

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ABSTRACT (250 words)

Nerve injuries are common and full recovery is challenging. The available therapeutic interventions mostly rely on surgical procedures, which cannot guarantee complete regeneration of the injured nerve and sufficient restoration of function. Among other factors, the slow rate of axonal growth hampers the functional recovery. Development of new approaches to discover underlying mechanisms that may accelerate axonal growth is needed to overcome the current limitations and augment available treatments of nerve injury. Moreover, combining the available methods with new mechanisms that can accelerate axonal growth at the injury site, can lead to the desired breakthrough in this field.

This project will focus on discovery of a novel mechanism that can accelerate axonal growth via calcium signaling and by activation of the heat sensitive and calcium permeable ion channel, TRPV1. We rely on the magnetothermal approach in which magnetic nanoparticles (MNPs) dissipate heat upon exposure to alternating magnetic fields (AMFs) with high frequencies and low amplitudes (~10s mT). By creating scaffolds bearing MNPs and dissipating heat under alternating magnetic fields, we will examine the role of Schwann cells in TRPV1-depedednt axonal growth within a co-culture model. We will employ those results to our previously established model of dorsal root ganglion explant, where accelerated axonal elongation was observed under magnentothermal stimulation.

We envision, that wireless magnetothermal control of calcium influx will advance understanding of calcium-dependent pathways involved in axonal growth, while offering a minimally invasive strategy to enhance nerve regeneration following injury using three-dimensional implants or combined with other intervention methods.

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INTRODUCTION

Nerve injury is a major health problem resulting from a traumatic event to the nerve. When such a physical injury occurs, it results in axotomy, where the axon is dissociated from its cell body. This dissociation is critical, and impede the regeneration process due to the extreme length of the axon in relation to its neuronal cell body. Shortly after the injury a Wallerian degeneration process starts which results in limited axonal regeneration[1]. There are limiting factors which impede the full recovery such as the severity of the injury, the patient's age and the time elapsed from the trauma to the start of intervention[1-3].

The most common strategies to bridge the gap between the proximal and distal end at the injury site, include autografts, nerve guiding scaffolds and cell therapy[1,4,5]. Recent efforts demonstrated that discovery of new methods and mechanisms to accelerate axonal growth rate holds great potential for promoting axonal regeneration. Several recent examples include optogenetic stimulation or electrical stimulation[6-9]. However, despite their promise, the mechanism of action in those methods is not fully known, and their translation to future therapeutic interventions is limited by the need of transgenes or hardware implantation at the injury site, especially challenging in injured organs and when immediate intervention is required. ***In a previous study, I discovered that calcium influx mediated through activation of calcium permeable ion channels, accelerate axonal elongation[10]***. Specifically, I developed a method to trigger the transient receptor potential vanilloid family member 1 (TRPV1)[11] which is a non-selective calcium permeable cation ion channel activated by capsaicin, temperatures > 41.5±1.1ºC and pH values < 5.9[12,13]. Previous studies demonstrated that balancing of intercellular and extracellular calcium levels promote axonal growth via regulation of the secretion of brain-derived neurotrophic factor (BDNF)[14] and netrin-1[15] and the formation of the growth cone[16]. Moreover, activation of neurons by capsaicin was shown to accelerate axonal growth, which was

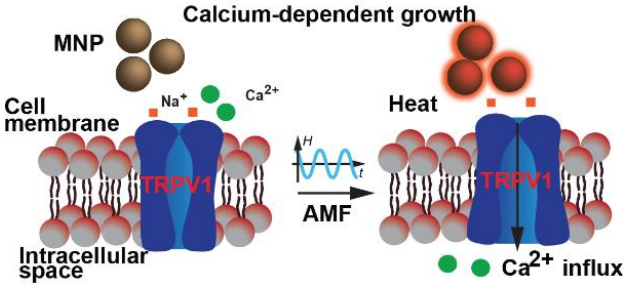

Figure 1: Mangetothermal stimulation of TRPV1 to induce calcium-dependent growth

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attributed to activation of the protein kinase A pathway due to TRPV1-mediated Ca^{2+} influx [17]. While promising, relying on capsaicin is dose dependent, involves side effects and lacks spatial resolution. Instead, our method relies on magnetic nanoparticles (MNPs) of iron oxide Fe_3O_4 in a size of 20-22 nm which demonstrate hysteretic heating when exposed to alternating magnetic fields (AMFs) with high frequency (100-600KHz) and low amplitudes (10-60 mT), thus reaching efficiently the temperature threshold of TRPV1 (**Fig. 1**).

Using dissipated heat from the MNPs, we proved that magnetothermal triggering of TRPV1 promotes axonal growth in *in vitro* dorsal root ganglion (DRG) explant model of peripheral nerve tissue, which endogenously express the ion channel TRPV1[10]. This approach offers opportunity for remote activation of the injured site, without the use of transgenes or hardware, and with local triggering with high spatial and temporal resolutions. Its high specificity to TRPV1 offers new mechanistic investigation on the role of TRPV1 in promoting axonal growth.

Schwann cells (SCs) play a critical role in modulating axonal regeneration via de-differentiation to progenitor-like cells, breaking of the myelin sheaths and participation in the Wallerian degeneration process[18,19]. When injury occurs the number of SCs in the area decreases, which prevents their ability to accelerate the regeneration process. In our preliminary results, we identified that activation of TRPV1 in DRG explant model leads to accelerated SC migration from the DRG body[10]. However, it is non-known yet whether activation of TRPV1 in neurons leads to this migration or it is a similar calcium signaling process in SCs.

SPECIFIC AIMS

This proposal aims to achieve axonal regeneration upon nerve injury. Based on our previous demonstration that calcium signaling mediated via TRPV1 activation accelerates axonal elongation, we will examine the role of SCs migration as well as establish a three-dimensional (3D) model. The advantages of the 3D model system are twofold: 1) it mimics better the natural cell environment unlike our previous demonstration in a 2D culture. 2) It paves the way towards future therapeutic interventions of implant transplantation at the injury site. Our aims are:

Aim 1: Design three-dimensional polymeric magnetic scaffold embedded with magnetic matrix and co-cultured neuronal cells and Schwann cells (SCs).

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Aim 2: Examine TRPV1 activation via calcium imaging comparing activation of neuronal cells and SCs in co-culture models.

Aim 3: Examine axonal growth upon activation of co-culture model of neuronal cells and SCs versus DRG explant model

METHODS

Aim 1: Design three-dimensional polymeric magnetic scaffold embedded with magnetic matrix and co-cultured neuronal cells and Schwann cells (SCs): In the first step, polymeric scaffolds will be fabricated using polycaprolactone (PCL), commonly used for creating nerve guiding scaffolds. Among its advantages is its ability to accommodate the MNPs. We will examine two approaches: 1) fabrication of PCL-MNPs scaffold where the MNPs are embedded within the polymer during synthesis. 2) fabrication of PCL scaffold and seeding cells with a magnetic supporting matrix. To achieve this goal, we will use thermally induced phase separation (TIPS) to fabricate the PCL scaffold[20], which allows creation of porous structure with modified properties (for example porosity and mechanical properties). For creation of PCL-MNP scaffolds, surface functionalized MNPs will be incorporated within the polymer during synthesis. Upon synthesis of the scaffolds, we will perform calorimetry measurement in a custom designed electromagnet coil that allows triggering heat dissipation from MNPS within 3D constructs and was developed in our previous study (funded by the Zimin institute, see progress report attached). Heat dissipated within the scaffold in both fabrication procedures will be assed and optimized for the purpose of this proposal. In the second step, we will create primary neuronal cultures of neurons dissociated from the DRG explants and primary culture for SCs[21]. Cells will be seeded within the scaffolds separately or as co-culture. Seeding conditions will be optimized in terms of cell number, ratio in the co-culture, cells viability within the scaffold with and without heat stimulation (and in the presence of MNPs). TRPV1 expression in both cell types will be quantified via immunostainings[10].

Aim 2: Examine TRPV1 activation via calcium imaging comparing activation of neuronal cells and SCs in co-culture models: Our preliminary data suggests that TRPV1 activation in the DRG explant model resulted in calcium influx that led to accelerated axonal growth. Therefore, in order to determine the effectiveness of the 3D system and in order to be able to examine the

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contribution of SCs migration in promoting the axonal growth, we will perform a series of calcium imaging experiments under the magnetothermal effect where TRPV1 activation of the cells will be examined via calcium influx. We will use the calcium indicator Fluo-4, previously employed in our TRPV1 activation demonstration and examine calcium influx to the cells embedded in the magnetic scaffold. We will compare the response of separate culture versus the co-culture. Immunostaining will be used to identify the responding cells within the co-culture system. To perform those experiments we will use our self-designed electromagnetic coil, which also allows performing simultaneous calcium imaging and magnetothermal stimulation. TRPV1 antagonist capsazepine will be employed to assure specification to TRPV1.

Aim 3: Examine axonal growth upon activation of co-culture model of neuronal cells and SCs versus DRG explant model

Based on the results from the previous two aims we will examine axonal growth upon activation of TRPV1 in the 3D model system in the following groups: 1) single cell culture 2) co-culture system of neurons and SCs 3) DRG explant model (with comparison to our preliminary results in 2D culture). To examine axonal elongation we will perform immunostaining for cytoskeletal elements (neurofilaments) and quantify using our self-written image analysis algorithm. The results of the previous aims will guide us in determining the seeding ratio, the stimulation parameters, the role of SCs and examination in the DRG explant model.

PRELIMINARY RESULTS

We previously created PCL magnetic scaffold where the MNPs were embedded within the polymeric matrix using the TIPS method (**Fig. 2A**, small image). This scaffold was exposed to alternating magnetic fields with parameters of *frequency*=150 kHz and *amplitude*=35 kA/m, in agreement

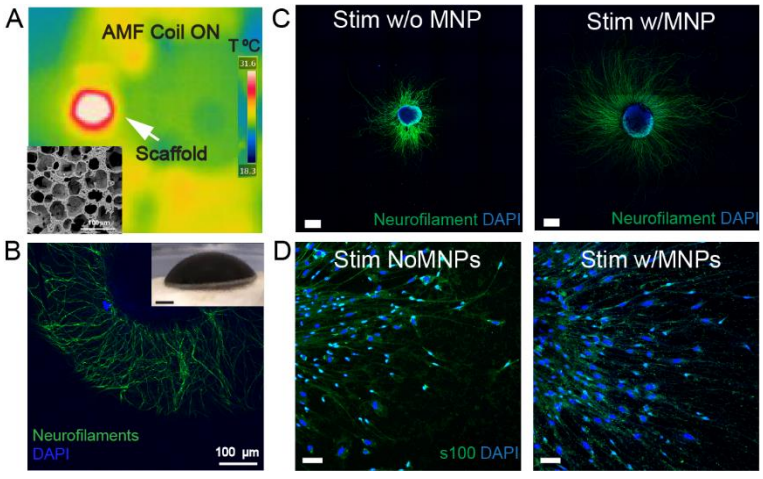

Figure 2: Preliminary results

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with the field parameters enabled in our new self-designed coil. Imaging with Infra-Red camera demonstrated the temperature increase within the scaffold (**Fig. 2A**). Moreover, we were able to embed our MNPs within Matrigel matrix, which also exhibited temperature increase upon exposure to AMFs and we were able to demonstrate good viability and growth of DRG explants within this system even after repeated AMFs stimulations (**Fig. 2B**). Moreover, we calibrated and demonstrated the needed magnetothermal stimulation parameters to accelerate axonal growth in 3D explant model, which also exhibited enhanced SCs migration (**Fig. 2C,D)**. Moreover, we verified the expression of TRPV1 in DRG using immunostaining and co-localization with neurons, cytoskeletal elements and SCs[10].

CONTRIBUTION OF THE PROPOSAL FOR A BETTER WORLD

Nerve injuries lead to lifelong disabilities with significant implications on the quality of life, affecting millions of people worldwide. The limiting factor is the inability to achieve full recovery and therefore the available intervention methods are lacking, and urging the research world to constantly look for new alternatives. A magnetothermal stimulation to accelerate axonal growth at the injury site offers a unique opportunity to integrate a new mechanism with the traditional intervention approaches, where the rate of axonal elongation will be controlled remotely in a minimally invasive manner. It can be combined either in a cell therapy treatment or as external modulation of the injured site with or without additional polymeric scaffold that can fill the gap in the injured nerve. Moreover, unlike previous modulation approaches that accelerated axonal growth such as optogenetic and electrical stimulation, here we propose a novel mechanism that can activate specific cell populations. As a proof of principal, we are planning not only to decipher the role of SCs migration in this mechanism but also to demonstrate the method in a 3D bioengineered design model. Lastly, the proposed approach is promising due to the use of AMFs signals, which offer safe, and unattenuated penetration to deep organs bearing negligible magnetic susceptibility. The magnetic stimulation parameters chosen for this project are in agreement with the field amplitude-frequency limit defined as $5{\cdot}10^9$ A/m·s, assuring safe stimulation with no further damage to the surrounding tissues and with a local effect only in the implant area.

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Request for a second year funding from the Zimin institute

1. Detailed description of the 1st year achievements

In the **first year project**, we aimed to develop **a small size magnetic coil device to produce alternating magnetic fields that can stimulate transplanted cells within magnetic bio-electronic implants**. Our goal was to use this novel system for remote control on implanted cells to replace malfunctioning organs. We focused on triggering implanted cells that bear thermally sensitive ion channels and to pioneer the combination of cell therapy with bioelectronic medicine approaches. To achieve this goal, over the past 6 months we designed an electromagnet coil that is capable of producing those magnetic field parameters. We performed thorough calculations of the required parameters to achieve this design with relevant simulation that will predict the magnetic field experienced by the sample. A driving circuit was designed, to drive the electromagnet at resonance frequency. **Figure 1** demonstrates the constructed electromagnet with the designed circuit and a simulation showing the signal attenuation matching the desired frequency of 150 kHz. This coil is currently in his final steps to achieve full functioning.

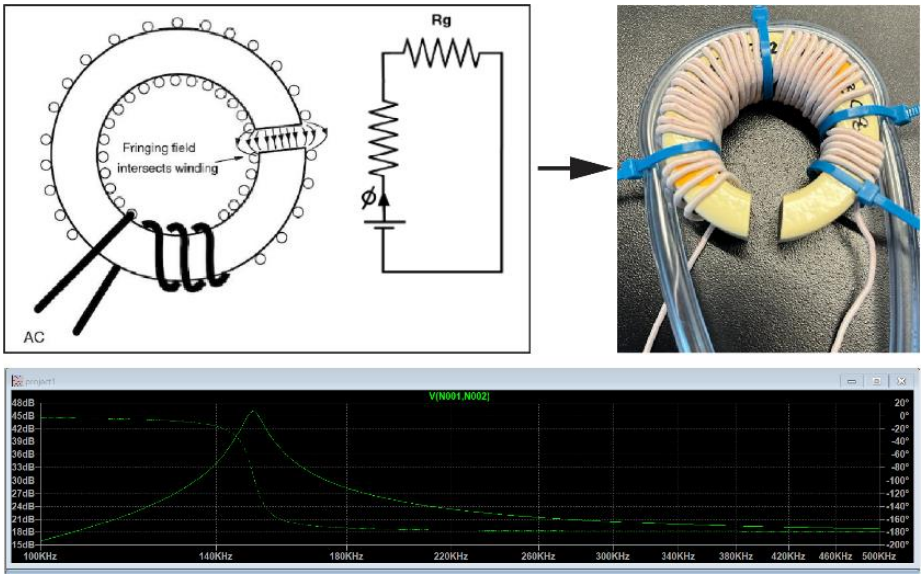

Figure 1: design and assembly of electromagnet coil

In parallel to the coil building, we created a magnetic Matrigel® that was capable of maintaining cells for a prolonged time of the experiments. We are now working on combining those two systems with adrenal cell culture to achieve remote release of cortisol from implanted cells.

***Manuscript describing heat dissipation in magnetic gels, while stimulated in the electromagnet is under preparation.*

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2. Request for a second year funding

We apply for a second year funding from the Zimin institute in order to initiate a novel project for accelerating nerve growth to treat nerve injuries, related to the call for bioconvergence and bioenegineering proposals.

In the previous project, submitted under the call for medical equipment, we focused on the design and assembly of a new electromagnet coil that can stimulate bioelectronic implants with specific alternating magnetic fields parameters of high frequencies and 10s of mT amplitudes. We proposed to examine the function of that magnetic coil on our previously established model of adrenocortical cells that release cortisol rapidly under the effect of the magnetothermal stimulation.

The current proposal will use this electromagnet device and setup for developing a bioengineered design for accelerating nerve growth. The nature of the current proposal will be different and will focus on scaffolds design for peripheral nerve injury and establishment of new mechanism and approach to accelerate neuronal growth in three-dimensional implants while investigating the role of Schwann cells in this mechanism. It will broaden the previous project via demonstration of a biological application that will use the same device developed last year. With that, we believe that we will advance the field of magnetothermal stimulation to develop new biological applications. We will expose different disciplines to the approach, which will lead to fruitful studies and novel therapeutic interventions with magnetic nanomaterials.

Dekel Rosenfeld - CV

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ACADEMIC APPOINTMENTS

Tel Aviv University

Senior Lecturer	Biomedical Engineering Department	2022-current

Massachusetts Institute of Technology

Research Scientist	Research Laboratory of Electronics, McGovern Institute for Brain Research	2020-2021
Postdoctoral Associate	Research Laboratory of Electronics,McGovern Institute for Brain Research	2016-2020

Technion, Israel Institute of Technology

Postdoctoral Scholar	Biomedical Engineering Department	2014-2015

EDUCATION

Technion, Israel Institute of Technology

Ph.D. in Biomedical Engineering	2009-2014
M.Sc. in Biomedical Engineering	2008-2009
B.Sc. in Biomedical Engineering, **cum laude**	2003-2007

HONORS

Zuckerman Faculty Scholars	2021
Travel grant award for postdoctoral fellows, Ilanit	2020
NIH BRAIN Initiative Trainee award	2018
Israel women in science award VATAT	2017,2018
MIT-Technion Fellowship for postdoctoral research	2016-2018
Katzir Fellowship for short term internship abroad, Boston, MA.	2012
Ed Sattel fellowship for outstanding PhD students	2008-2013
Dean's list for academic achievement for 5 semesters of undergraduate studies at the Technion	2003-2007
Award of the Israel Stem Cell Society	2013
Excellence in Teaching Award of the Technion	2012, 2013
Diploma with honors (**cum laude**), Biomedical Engineering Department, Technion	2007

TEACHING EXPERIENCE

Lecturer, Tel Aviv University, "Programming 2 in MATLAB", Biomedical Engineering	2022-current
Guest lecture, MIT course 3.001 "Intro Materials Science & Engineering"	2019-2021
Guest lecture, MIT course 9.123 / 20.203 "Neurotechnology in action"	2018,2019
Teaching assistant, Department of Biomedical Engineering, Technion	2009-2013

MENTORING EXPERIENCE

Current lab members: Lab manager, MSc students (2), Undergraduate students (4)

Supervised 4 undergraduate students in the MIT UROP program. Anikeeva lab. MIT	2016-2020
Supervised a graduate student from the MIT-Imperial college program. Anikeeva lab, MIT	2017-2018
Supervised an undergraduate student in MIT Summer Research Program (MSRP)	2017
Supervised an undergraduate student from Georgia Tech in the summer research program	2016
Supervised 3 projects for undergraduate thesis projects. Technion (4 students)	2011-2013

PUBLICATIONS (selected out of 26)

1. **Dekel Rosenfeld**, Hannah Field, Ye Ji Kim, Karen Ka Lam Pang, Keisuke Nagao, Florian Koehler, Polina Anikeeva. 2022. Magnetothermal Modulation of Calcium-Dependent Nerve Growth. Advanced Functional Materials. 0224558
2. Lisa Y Maeng*, **Dekel Rosenfeld***, Gregory J Simandl, Florian Koehler, Alexander W Senko, Junsang Moon, Georgios Varnavides, Maria F Murillo, Adriano E Reimer, Aaron Wald, Polina Anikeeva, Alik S Widge. 2022. Probing Neuro-Endocrine Interactions Through Remote Magnetothermal Adrenal Stimulation. Frontiers in Neuroscience. 16. ***Equal contribution**

3. Sarah-Anna Hescham, Po-Han Chiang, Danijela Gregurec, Junsang Moon, Michael G Christiansen, Ali Jahanshahi, Huajie Liu, **Dekel Rosenfeld**, Arnd Pralle, Polina Anikeeva, Yasin Temel. 2021. Magnetothermal nanoparticle technology alleviates parkinsonian-like symptoms in mice. Nature communications. 12 (1), 1-10
4. Marc-Joseph Antonini, Atharva Sahasrabudhe, Anthony Tabet, Miriam Schwalm, **Dekel Rosenfeld**, Indie Garwood, Jimin Park, Gabriel Loke, Tural Khudiyev, Mehmet Kanik, Nathan Corbin, Andres Canales, Alan Jasanoff, Yoel Fink, Polina Anikeeva. 2021. Customizing MRI-Compatible Multifunctional Neural Interfaces through Fiber Drawing. Advanced Functional Materials. 2104857
5. Anthony Tabet, Marc-Joseph Antonini, Atharva Sahasrabudhe, Jimin Park, **Dekel Rosenfeld**, Florian Koehler, Hyunwoo Yuk, Samuel Hanson, Jordan A Stinson, Melissa Stok, Xuanhe Zhao, Chun Wang, Polina Anikeeva. 2021. Modular integration of hydrogel neural interfaces. ACS Central Science. 7, 9, 1516–1523
6. Dena Shahriari*, **Dekel Rosenfeld*,** Polina Anikeeva. Emerging frontier of peripheral nerve and organ interfaces. Neuron. In press *Equal contribution
7. **Dekel Rosenfeld**, Alexander W. Senko, Junsang Moon, Isabel Yick, Georgios Varnavides, Danijela Gregureć, Florian Koehler, Po-Han Chiang, Michael G. Christiansen, Lisa Y. Maeng, Alik S. Widge and Polina Anikeeva. 2020. Transgene-free remote magnetothermal regulation of adrenal hormones. Science Advances. 6 (15), eaaz3734.
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10. Danijela Gregurec, Alexander Senko, Andrey Chuvilin, Pooja Reddy, Ashwin Sankararaman, **Dekel Rosenfeld**, Po-Han Chiang,; Francisco Garcia, Ian Tafel, Georgios Varnavides, Eugenia Ciocan, Polina Anikeeva. 2020. Tuning the magnetic vortex state in magnetite nanodiscs for remote control of biological signaling. ACS Nano. 14 (7), 8036-8045.
11. **Dekel Rosenfeld**, Shira Landau, Yulia Shandalov, Noa Raindel, Erez Shor, Yaron Blinder, Herman Vandenburgh, David Mooney and Shulamit Levenberg. 2016. Morphogenesis of 3D vascular network is .regulated by tensile forces. Proc Natl Acad Sci U S A. 113(12): 3215–322.
12. **Dekel Dado-Rosenfeld**, Itai Tzchori, Amir Fine, Limor Chen-konak and Shulamit Levenberg. 2014. Tensile forces applied on a cell-embedded 3D scaffold can direct early differentiation of embryonic stem cells toward the mesoderm germ layer. Tissue engineering Part A. 21 (1-2), 124-133.
13. **Dekel Dado** and Shulamit Levenberg. 2009. Cell–scaffold mechanical interplay within engineered tissue. Seminars in Cell and Developmental Biology. 20 (6), 656-664.

Patents

1. J Avesar, S Levenberg, **D Rosenfeld**, YJ Blinder. Antimicrobial susceptibility test kits. US Patent App. 16/486,879
2. P Anikeeva, **D Rosenfeld**, A Widge. Therapeutic uses of controlled adrenal release. University of Minnesota patent.

SELECTED ABTRACTS AND INVITED TALKS (selected out of 24)

1. Invited Keynote speaker: Nano Bio Med Conference. Spain , 2022
2. Oral presentation: 2022 Material Research Society conference, Boston, 2022
3. Oral presentation: 2022 Material Research Society conference, Hawaii. 2022
4. Invited seminar, NYU Langone Health, New York, NY, September 2021
5. Oral presentation: “Neurotech in Action” symposium, MIT, Cambridge, MA, 2020
6. Oral presentation: 2019 Biomedical Engineering society conference, Philadelphia, PA, 2019
7. Research highlight talk: 2018 BRAIN Initiative PI Meeting, DC, 2018
8. Oral presentation: 2018 Material Research Society, Phoenix, AZ, 2018
9. Invited speaker: 2017 Mayo Clinic Symposium on the BRAIN Initiative, Rochester, MN, 2017
10. Oral presentation: 4th TERMIS World Congress. Boston, MA, USA. September 2015
11. Oral presentation: 5th International Conference on Tissue Engineering, Kos, Greece, June 2014

BUDGET

	Requested	Matching	Total
Lab manager	9,000$	3,000$	12,000$
Postdoc	24,000$	8,000$	32,000$
Shared facilities	9,000$	3,000$	12,000$
Equipment	24,000$	8,000$	32,000$
Consumable	6,000$	2,000$	8,000$
Publications	3,000$	1,000$	4,000$
Total	75,000$	25,000$	100,000$

BUDGET JUSTIFICATION

Personnel

The team will include the PI, a lab manager and a postdoc. The PI will supervise the work and perform training on scaffold and MNPs synthesis and fabrication and electromagnet coil operation.

The lab manager will be responsible for ordering supplies and consumable, day-to-day lab operation, establishing biological experiments, immunostaining and assist with protocols and microscopy.

The postdoc will be with engineering background and knowledge in materials design specifically synthesis of nanoparticles and fabrication of polymeric scaffolds. The postdoc will functionalize the nanoparticles, establish the nanocomposites, test them with cell cultures and perform in vitro calcium imaging experiments. The funds for the lab manager are based on dedicating 15% of the time for this project. The funds requested for the postdoc are according to the standard fellowship at Tel Aviv University.

Shared facilities

The equipment in the Center for Nanoscience and Nanotechnology in Tel Aviv University will be used for nanoparticles and scaffold characterization.

Equipment

The budget will be used to purchase sample holders for performing calorimetry of magnetic scaffolds. Moreover, we plan to purchase a standard vibrating sample magnetometer operating at room temperature.

Consumable

The budget will be used to purchase general lab supply as well as biological and chemical materials for synthesis and biological work with cell cultures. This includes polymers, solvents and chemical for the chemical work and biological reagents (cell media, viability assay, reagents for cell dissociation).

Publications

This project is expected to produce 1-2 publications in high impact open access journals and the budget will be used for publication costs and manuscript editing.

Iby and Aladar Fleischman
Faculty of Engineering
Tel Aviv University

הפקולטה להנדסה
ע"ש איבי ואלדר פליישמן
אוניברסיטת תל-אביב

Jan 29th, 2023
Prof. David Mendelovitch
Director
Zimin Institute
Faculty of Engineering
Tel Aviv University

Dear David,

Re: Endorsement letter for Dr. Dekel Rosenfeld

I hereby support and endorse the application of Dr. Dekel Rosenfeld, a young faculty member in my department, on "**Bioengineered three-dimensional design to promote neuronal regeneration**" submitted to the 2023 'Zimin Institute for Engineering Solutions Advancing Better Lives' call.

Dekel's proposal will focus on the development of remote external stimulation with alternating magnetic fields of three-dimensional magnetic nanocomposites co-culture neuronal models, that will advance the field of neural regeneration and for treating nerve injuries.

The proposal fits with the 2023 Zimin's call for bioconvergence and bio-engineering

I wish Dekel good luck with her application.

Sincerely yours,

Prof. Natan T. Shaked,
Chair; Department of Biomedical Engineering
The Iby and Aladar Fleischman Faculty of Engineering
Tel Aviv University

N. Shaked