An integrated engineering-computational-biological (ECB) approach to unravel molecular dysfunction in Parkinson's disease

Principal Investigators: Dr. Ben M. Maoz[1,2], Prof. Roded Sharan[3] and Prof. Uri Ashery[2,4]

[1]Department of Biomedical Engineering; [2]Sagol School of Neuroscience; [3]Blavatnik School of Computer Science; [4]School of Neurobiology, Biochemistry and Biophysics; Tel Aviv, Israel TAU

Abstract:

In this cross campus proposal, our ultimate goal is to develop a human relevant *in vitro* platform for studying Parkinson's disease (PD), and to use it for identifying PD-associated abnormal pathways using patient specific differentiated cells. To achieve this ambitious goal, we will pursue the following aims (**Figure 1**): **a)** Develop an isogenic human neurovascular (NVU) platform on a chip (NVU-on-a-Chip) including specific biosensors, which will enable us to assess neuronal functionality and pathology. **b)** Perform systematic measurements of gene expression levels and functional response under common PD mutations. **c)** Derive predictive models of cellular response to mutations. The research team consists of an expert in NVU-on-a-Chip and biosensors (Ben Maoz, Bioengineering), an expert in neuroscience and cellular and molecular aspects of Parkinson's disease (Uri Ashery, Neurobiology) and an expert in computational modeling (Roded Sharan, Computer Science). The outcome of our integrated ECB framework will be: **(i)** novel human personalized platform for drug and disease assessment, and **(ii)** newly identified genomic variations, cellular PD-associated phenotypes, and disease pathways that can be used to develop novel and specific therapeutic strategies.

Scientific background:

In recent years there is great progress in designing *in vitro* models, yet standard *in vitro* tools mainly use primary cells from rodents or cell-lines, which suffer from inter-species differences and do not reflect the human complexity. Moreover, they lack physiochemical and mechanical cues and are not able to mimic tissue-tissue interactions. This is even more challenging when we examine complex systems like the brain which consist of multiple cell types. Recently, a new concept for studying human relevant physiology was developed. This concept, known as Organ-on-a-Chip (OoC), consists of human-specific tissue in a microfluidic chip that mimics organ functionality by recapitulating the multicellular architectures, vascular-parenchymal tissue

interfaces, chemical gradients, mechanical cues, and vascular perfusion of the body. This approach can produce levels of tissue and organ functionality, in addition to mimicry of human disease states, not possible with conventional 2D and 3D iPSCs culture systems [1–7]. In addition, OoC promotes maturation of human cells, providing a human-disease relevant *in vitro* model for the investigation of mutation effects on cellular processes and pathways [1,8–10].

As we are interested to study neurodegenerative disease in a human relevant system we are limited by the cell source, as it is extremely challenging to get primary cell from the human brain which can be cultured in a dish. To overcome this challenge, a new tool, known as induced human pluripotent stem cells (ihPSC) was developed, which enables us to create any cell type from a patient skin biopsy. While this method gains popularity, it is still not used to its full potential as most models either contain only one cell type or integrate multiple cell types that do not share the same genetic background (i.e., non-isogenic). A primary goal of this proposal is to create advanced human relevant *in vitro* isogenic model of the human neurovascular unit (NVU) – Iso-NVU-on-a-Chip (which include the blood-brain-barrier and neurons), which will be used as an infrastructure for the proposed PD research.

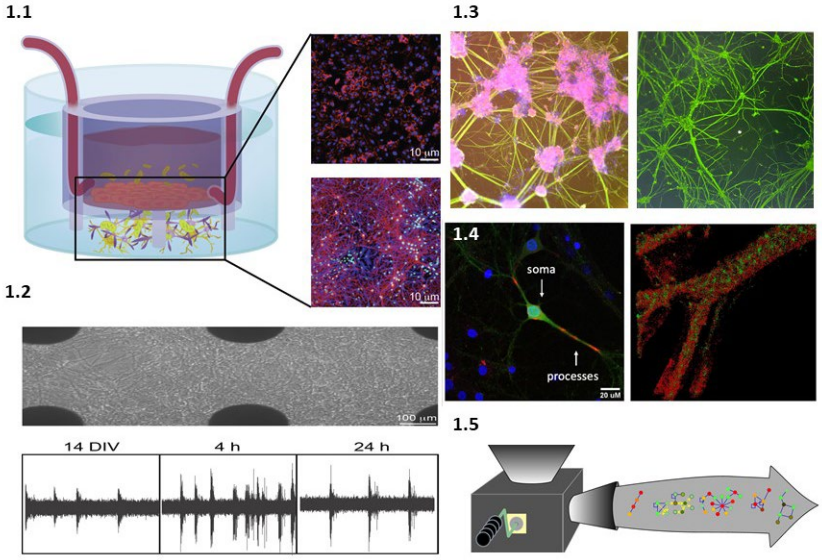
A disease phenotype is rarely the consequence of an abnormality in a single gene or protein but rather reflects a multitude of pathobiological processes connected in a complex network of protein-protein interactions (PPIs). While current modeling approaches like Ingenuity Pathway Analysis focus on known signaling pathways, our ANAT modeling framework can be used to infer yet-unknown pathways with similar characteristics to known ones [11], thus providing a mechanistic explanation of the disease and serving as an infrastructure for subsequent predictive modeling. *GBA-N370S* and *LRRK2-G2019S* are the most common genetic mutations associated with PD, especially in the Ashkenazi Jewish population. These mutations are known to perturb cellular clearance and trafficking pathways associated with PD. However, clinical data suggest that although *PD-GBA-1* is associated with a more severe phenotype than *PD-LRRK2* in most domains, PD patients harboring dual *LRRK2*/*GBA-1* mutations exhibit milder phenotypes. Therefore, ***we hypothesize*** that mutations in these genes lead to abnormal protein-protein interactions (PPIs) and perturbation of specific neuronal functions. By integrating the NVU with systematic gene expression, functional measurements and PPI network models we will aim to uncover the central

pathways of the disease and build computational models that can predict functional impact of genetic mutations.

Research plan:

The methodology will be divided into **a) platform development-** Developing an isogenic human neurovascular (NVU) platform on a chip (NVU-on-a-Chip) including specific biosensors, which will enable us to assess neuronal functionality and pathology; **b) platform exploitation -** perform systematic measurements of gene expression levels and functional response under common PD mutations; and **c) model development** – apply network biology and machine learning techniques to assess how known genetic mutations lead to PD pathology and derive predictive models of cellular response to mutations.

a) Platform development - The Iso-NVU-on-a-Chip-platform – this will include the chip and the iPSC development. *The chip* will be based on the previous Neurovascular Unit-Chip that was developed by the Maoz lab (**Fig. 1.1**). This will be integrated with smart Chips that can measure the electrical activity of neurons, as they are equipped with multi-electrode array (MEA) (**Fig. 1.2)** and will be especially designed and integrated with super resolution microscopy (SRM) system developed by the Ashery and Maoz labs (**Fig. 1.4**). *The isogenic NVU* cells will be developed according to protocols that were developed by Shusta for isogenic brain microvasculature and neurons, which were already



Iso-NVU-on-a-Chip-platform 1.1 BoC platform. **1.2** MEA allows recording of electrical activity of neurons in the NVU-on-a-Chip platform. **1.3** iPSC differentiated into dopaminergic neurons can be grown on the NVU-on-a-Chip platform. **1.4** SRM imaging allow the detection of alpha synuclein aggregate from iPSC grown on NVU-on-a-Chip platform.**1.5** Disease modeling via protein-protein interaction network analysis.

implemented in our lab (**Fig 1.3** shows iPSC derived dopaminergic neurons). We will then use our Iso-NVU-on-a-Chip-platform to identify how specific mutation in the NVU can affect the cellular functionality. As a case study, we will look how mutations in *LRRK2*^{G2019S} and *GBA-1*^{N370S} lead to NVU dysfunction. This will be done with collaboration with Prof. Avi Or-Urterger, Prof. Nir Giladi and Dr. Orly Goldstein (Echilov Medical Center) that provided us with unique cohort of patients which has such mutations, and their genetic background is fully characterized. We will generate an Iso-NVU-on-a-Chip-platform from their cells. Specifically, iPSCs from a patient carrying GBA-N370S and a patient with double mutation GBA-N370S/ LRRK2-G2019S ***are already available*** and dopaminergic neurons are being generated these days.

b) Platform exploitation – As a next step, we will use our Iso-NVU-on-a-Chip-platform to identify how specific mutation in the NVU can affect the cellular functionality. We will examine the NVU functionality by using tools such as: trans-epithelial-electrical-resistance (TEER, for endothelial permeability), super resolution microscopy (to identify aggregation of α-Synuclein (which is the hallmark of PD), and MEA, **Fig. 1.2, 1.4**), for neuronal functionality). We will then profile the gene expression of the generated cells and identify differential genes for each of the cellular models.

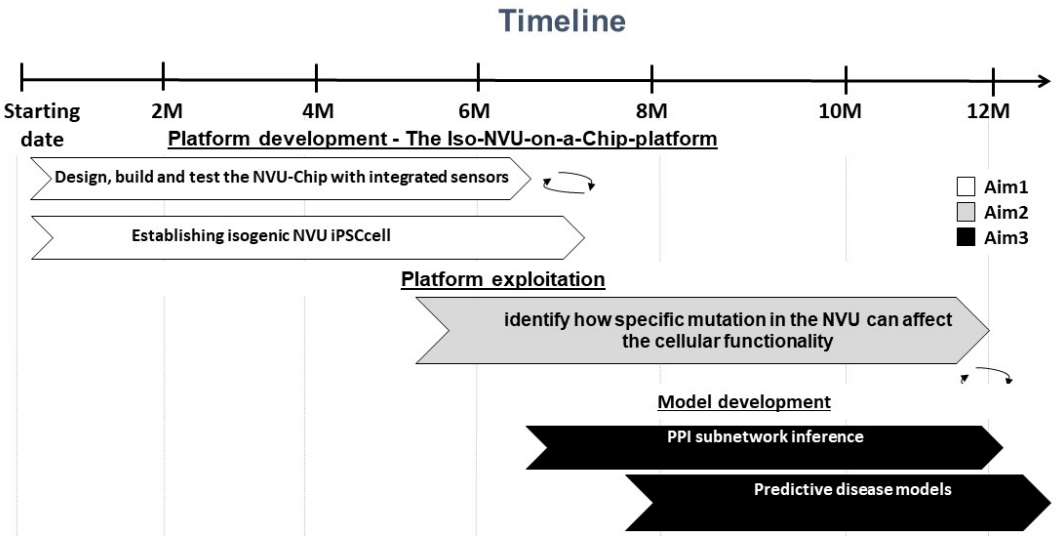
c) Model development – We will project the differential expression data, termed the responding genes, onto a neurodegenerative disease-specific PPI network [12] (**Fig. 1.5**) to identify novel disease-associated components. This will be done in PD-*LRRK2* , PD-*GBA-1* and double mutation PD-*LRRK2*-*GBA-1* patients. For each condition, we will apply our in-house ANAT framework to obtain a compact and high-scoring subnetwork that connects the causal disease proteins (LRRK2, GBA-1 or both, as appropriate) to the responding proteins. The subnetworks will reveal novel pathways involved in PD and their average expression levels will be used to build a predictive, gradient boosting model of functional response. The proteins networks revealed in this study can uncover widespread protein abnormalities and aggregation common to many neurodegenerative diseases as we have recently demonstrated [12].

While this project is very ambitious, and aims to accomplish a lot within the timeline of the proposal (1 year), it is important to note, that the strong synergy between the 3 groups was

previously proved when we teamed up to identify what is the effect of SARS-CoV-2 proteins on vascular permeability. Within one year we developed a vascular model and integrated it with a PPI, identified the significant SARS-Cov-2 proteins which effect the vasculature. The project was published in elife (https://elifesciences.org/articles/69314) within a year. This demonstrates the synergy and the strength of the team, and the feasibility to achieve this ambitious goal within one year.

Resources: Our team has all the necessary equipment; Maoz's lab: chemical lab, potentiostate, confocal microscope, multi-electrode array, 4X 3D printers and tissue culture equipment. Ashery's lab: tissue culture, super resolution microscopy, virus facility and Sharan's lab has several multiple-core computer servers that could run the suggested computations. In addition, Maoz and Ahsery established an iPSC core facility for neuronal differentiation. Nevertheless, we have full access to the university core facilities (nano center, imaging facility, machine shop) and in the Interdepartmental Equipment Facility (TZABAM).

Manpower, collaborations and timeline: Our interdisciplinary research group consists of biologists, electrical engineering, biomedical engineering, computer scientists and neuroscientist. The project will be a joint effort between 3 labs which are pioneers in their respective fields.



References

1. Maoz BM, Herland A, FitzGerald EA, et al. A linked organ-on-chip model of the human neurovascular unit reveals the metabolic coupling of endothelial and neuronal cells. *Nat Biotechnol*. 2018;36(9):865-874. doi:10.1038/nbt.4226
2. Bhatia SN, Ingber DE. Microfluidic organs-on-chips. *Nat Biotechnol*. 2014;32(8):760-772. doi:10.1038/nbt.2989
3. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014;32(1):40-51. doi:10.1038/nbt.2786
4. Booth R, Kim H. Characterization of a microfluidic in vitro model of the blood-brain barrier (μBBB). *Lab Chip*. 2012;12(10):1784-1792. doi:10.1039/c2lc40094d
5. Naik P, Cucullo L. In vitro blood-brain barrier models: Current and perspective technologies. *J Pharm Sci*. 2012;101(4):1337-1354. doi:10.1002/jps.23022
6. Nishikawa SI, Goldstein RA, Nierras CR. The promise of human induced pluripotent stem cells for research and therapy. *Nat Rev Mol Cell Biol*. 2008;9(9):725-729. doi:10.1038/nrm2466
7. Prabhakarpandian B, Shen MC, Nichols JB, Mills IR, Sidoryk-Wegrzynowicz M, Aschner M, Pant K. SyM-BBB: A microfluidic blood brain barrier model. *Lab Chip*. 2013;13(6):1093-1101. doi:10.1039/c2lc41208j
8. Sances S, Ho R, Vatine G, West D, Laperle A, Meyer A, Godoy M, Kay PS, Mandefro B, Hatata S, Hinojosa C, Wen N, Sareen D, Hamilton GA, Svendsen CN. Human iPSC-Derived Endothelial Cells and Microengineered Organ-Chip Enhance Neuronal Development. *Stem Cell Reports*. 2018;10(4):1222-1236. doi:10.1016/j.stemcr.2018.02.012
9. Vatine GD, Barrile R, Workman MJ, Sances S, Barriga BK, Rahnama M, Barthakur S, Kasendra M, Lucchesi C, Kerns J, Wen N, Spivia WR, Chen Z, Van Eyk J, Svendsen CN. Human iPSC-Derived Blood-Brain Barrier Chips Enable Disease Modeling and Personalized Medicine Applications. *Cell Stem Cell*. 2019;24(6):995-1005.e6. doi:10.1016/j.stem.2019.05.011
10. Jagadeesan S, Workman MJ, Herland A, Svendsen CN, Vatine GD. Generation of a human IPSC-based blood-brain barrier chip. *J Vis Exp*. 2020;2020(157).

doi:10.3791/60925

11. Signorini LF, Almozlino T, Sharan R. ANAT 3.0: a framework for elucidating functional protein subnetworks using graph-theoretic and machine learning approaches. *BMC Bioinformatics*. 2021;22(1). doi:10.1186/s12859-021-04449-1
12. Haenig C, Atias N, Taylor AK, et al. Interactome Mapping Provides a Network of Neurodegenerative Disease Proteins and Uncovers Widespread Protein Aggregation in Affected Brains. *Cell Rep*. 2020;32(7). doi:10.1016/j.celrep.2020.108050

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Roded Sharan

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

POSITION TITLE: Professor of Computer Science

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
Hebrew University, Jerusalem, Israel	BSc	07/1992	Mathematics & Computer Science
Hebrew University, Jerusalem, Israel	MSc	09/1995	Computer Science
Tel Aviv University, Tel Aviv, Israel	PhD	06/2003	Computer Science
University of California, Berkeley, CA	Post-doc	01/2005	Bioinformatics

Personal Statement

I am conducting bioinformatics research for almost 20 years and my main expertise is the analysis and modelling of protein-protein interaction networks with applications to deciphering disease mechanisms and predicting drug responses. My group has developed leading methods for network inference and modelling [1], network-based gene prioritization [2], network propagation based methods for genetic analysis [3] and network annotation methods [4]. A tool we have developed for protein pathway reconstruction is used by hundreds of labs world-wide [5]. On the thematic side, we have provided the first network descriptions of many basic processes including telomere length maintenance (in yeast and human), programmed cell death, Met-induced breast cancer, alternative splicing in colon cancer, the early secretory pathway and neurodegenerative diseases [6]. In addition, we developed methods for mutational signature analysis [7,8].

[1] N. Yosef, E. Zalckvar, L. Ungar, A. Kimchi, M. Kupiec, E. Ruppin and R. Sharan. Toward accurate reconstruction of functional protein networks. *Mol. Syst. Biol.* 2009; 5:#248.
[2] O. Vanunu, O. Magger, E. Ruppin, T. Shlomi and R. Sharan. Associating genes and protein complexes with disease via network propagation. *PLoS Comp. Biol.* 2010; 6:#e1000641.
[3] L. Cowen, T. Ideker, B.J. Raphael and R. Sharan. Network propagation: a universal amplifier of genetic associations. *Nature Reviews Genetics* 2017; 18:551-562.
[4] D. Silverbush and R. Sharan. A systematic approach to orient the human protein-protein interaction network. *Nature Communications* 2019; 10:1-9.
[5] N. Yosef, E. Zalckvar, A.D. Rubinstein, M. Homilius, N. Atias, L. Vardi, I. Berman, H. Zur, A. Kimchi, E. Ruppin and R. Sharan. ANAT: a tool for constructing and analyzing functional protein networks. *Sci Signal* 2011; 4: pl1.
[6] C. Haenig, N. Atias, A.K. Taylor, A. Mazza, M.H. Schaefer, J. Russ, S.-P. Riechers, S. Jain, M. Coughlin, J.-F. Fontaine, B.D. Freibaum, L. Brusendorf, M. Zenkner, P. Porras, M. Stroedicke, S. Schnoegl, K. Arnsburg, A. Boeddrich, L. Pigazzini, P. Heutink, J.P. Taylor, J. Kirstein, M.A. Andrade-Navarro, R. Sharan and Erich E. Wanker. Interactome Mapping Provides a Network of Neurodegenerative Disease Proteins and Uncovers Widespread Protein Aggregation in Affected Brains. *Cell Reports* 2020; 32,#108050.
[7] D. Wojtowicz, I. Sason, X. Huang, Y.-A. Kim, M. Leiserson, T. Przytycka and R. Sharan. Hidden Markov Models Lead to Higher Resolution Maps of Mutation Signature Activity in Cancer. *Genome Med.* 2019; 11:#49.

[8] I. Sason, Y. Chen, M. Leiserson and R. Sharan. A mixture model for signature discovery from sparse mutation data. *Genome Med.* 2021; 13:#173.

My full list of publications can be found at:
https://scholar.google.co.il/citations?user=64G5UgMAAAAJ&hl=en

Positions

2005-2007	Senior Lecturer, School of Computer Science, Tel Aviv University
2007-2014	Associate Professor, School of Computer Science, Tel Aviv University
2014-	Full Professor, School of Computer Science, Tel Aviv University

Honors

2002	Fulbright grant for post-doctoral studies, United-States Israel Educational Foundation
2002	Rothschild fellowship, Rothschild Foundation
2004	Best Paper by a Young Scientist award, RECOMB'04, San Diego, CA
2004	Alon fellowship, Israel
2007	Krill Prize, the Wolf Foundation
2010	Best Paper award, RECOMB'10, Lisbon, Portugal
2011	Distinguished young investigator, TAU
2012	Appointed to the Young Israel Academy for excellence in research
2014	Highly Cited Researcher, Thomson Reuters
2015	Kadar Family Prize for excellence in research
2016	Test of Time Award, RECOMB'16, Los Angeles, CA
2017	Test of Time Award, RECOMB'17, Hong Kong
2020	Test of Time Award, RECOMB'20, virtual

Community Service

- I am actively involved in promoting science and young scientists in Israel through my membership in the Young Israel Academy of Sciences and Humanities (2012-2017; served as a member of the executive committee 2013-2014).
- I am an active member of the Israeli Society for Bioinformatics and Computational Biology; I served as a board member 2015-2017, as president of the society 2014-2015, as vice-president 2012-2014 and as treasurer 2005-2008.
- I actively organize and chair international bioinformatics conferences. A selected set includes: Session organizer, CSHL Genome Informatics, 2005; Organizing committee chair of 11th Israeli Bioinformatics Symposium, 2008; Co-chair of "Protein interactions and molecular networks" track in ISMB 2010, 2013; PC chair of RECOMB 2014; Area Chair of "Systems Biology and Networks" in ISMB 2018; Co-chair of "Algorithms, biotechnologies and analysis for functional genomics data" at the Simons Institute in 2022; and Co-chair of CSHL Network Biology in 2021.
- I am currently serving on the steering committee of RECOMB. I served on several editorial boards including EMBO Reports (member of the advisory board); BMC Bioinformatics (Associate editor); Journal of Computational Biology and IEEE/ACM Transactions on Computational Biology and Bioinformatics (Associate editor).

Active Research Support

2018-2022: Logical modeling of protein networks**.** ISF, PI.
2019-2023: SECRET-Exploitation of the SECRETory pathway for cancer therapy. EU Horizon 2020, PI.
2020-2022: A comparative analysis of mutational processes in germline and soma. Koret Foundation, PI.
2020-2024: Elucidating epigenetic mechanisms that drive autism spectrum disorder and tailoring a personalized treatment. ISF – Israel Precision Medicine Program, PI.
2020-2024: Modeling Mutational Process Activity and Etiology in Cancer. BSF, PI.

BIOGRAPHICAL SUMMARY

NAME: Ashery, Uri

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

POSITION TITLE: Full Professor, Neurobiology

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
Hebrew University, Jerusalem	BSc	09/1990	Biology and Chemistry
Hebrew University, Jerusalem	PHD	04/1996	Neurobiology
Max Planck Institute, Göttingen	Postdoctoral Fellow	08/2001	Neurobiology

A. Personal Statement

I have been investigating the molecular mechanisms of synaptic transmission and plasticity over the last 20 years starting in my postdoctoral studies with Prof. Erwin Neher in Gottingen and in the last 19 years as an independent investigator at Tel Aviv University. During this time, my lab developed several approaches and opened new directions to understand the molecular mechanisms of vesicle priming and fusion using electrophysiology and TIRF measurements and developed new kinetic models that describe vesicle exocytosis. I have also applied optogenetic approaches to investigate molecular mechanism of hippocampal mossy fiber plasticity. Recently, we have started to implement dSTORM and super resolution microscopy techniques to study protein aggregation in neurodegenerative diseases. We are developing tools for characterization of protein aggregation like alpha synuclein in Parkinson's disease, or huntingtin protein in Huntington's disease. We use mouse model, skin biopsies from patients and human induced pluripotent stem cells and these tools can be used both for early diagnosis and for tracking disease progression and efficacy of treatment. On the administrative side, I have been leading the establishment and management of a unique and very successful eco system at Tel Aviv University – the Sagol School of Neuroscience – and therefore I have the expertise, leadership and motivation necessary to successfully coordinate and carry out the proposed project.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2013 - present	Full Professor, Neurobiology department, Tel Aviv University, Tel Aviv
2009 - 2012	Associate Professor, Neurobiology department, Tel Aviv University, Tel Aviv
2008 - 2009	Sabbatical Leave, Research associate, NIA, NIH, Baltimore, MD
2005 - 2009	Senior Lecturer, Neurobiology department, Tel Aviv University, Tel Aviv
2001 - 2005	Lecturer, Neurobiochemistry department, Tel Aviv University, Tel Aviv
1996 – 2001	Research Associate in Membrane Biophysics, Max Planck Institute, Göttingen

Other Experience and Professional Memberships

2018 - 2020	Head, Sagol School of Neuroscience, Tel Aviv University
2017- 2018	Sabbatical Leave, Research associate, NINDS, NIH, Bethesda, MD
2011- 2017	Head, Sagol School of Neuroscience, Tel Aviv University
2010 - 2012	Chair, Department of Neurobiology, Tel Aviv University
2007 - 2011	Head of the new Ph.D. program in Neurosciences, Tel Aviv University
2006 - 2006	Initiator of a new Ph.D. program in Neurosciences, Tel Aviv University
2004 - 2007	Head of a B.Sc. program for brain studies, Tel Aviv University

Honors

2018	The Rector best lecturers list (20 best lecturer out of 1000)
2006	The Bernard Katz Prize for Neurosciences, Israel Society for Neuroscience
2006	List of 10 best lecturers in the Life Sciences Faculty, Tel Aviv University
2005	List of 10 best lecturers in the Life Sciences Faculty, Tel Aviv University
2002	Dan David Prize, Tel Aviv University
1999	“Landau” prize for biology, Hebrew University
1995	"Intel-Deans" Prize for Excellency for Ph.D. students, Hebrew University
1992	Wolf prize for Ph.D. students, Wolf Foundation, Hebrew University
1988	Deans prize of Excellency for undergraduate students, Hebrew University

C. Selected Peer-reviewed Publications (Total: 71 journal papers)

1. Yizhar O, Lipstein N, Gladycheva SE, Matti U, Ernst SA, Rettig J, Stuenkel EL, Ashery U. Multiple functional domains are involved in tomosyn regulation of exocytosis. J Neurochem. 2007 Oct;103(2):604-16. PubMed PMID: 17666050.
2. Lipstein N, Sakaba T, Cooper BH, Lin KH, Strenzke N, Ashery U, Rhee JS, Taschenberger H, Neher E, Brose N. Dynamic control of synaptic vesicle replenishment and short-term plasticity by Ca(2+)-calmodulin-Munc13-1 signaling. Neuron. 2013 Jul 10;79(1):82-96. PubMed PMID: 23770256.
3. Ben-Simon Y, Rodenas-Ruano A, Alviña K, Lam AD, Stuenkel EL, Castillo PE, Ashery U. A Combined Optogenetic-Knockdown Strategy Reveals a Major Role of Tomosyn in Mossy Fiber Synaptic Plasticity. Cell Rep. 2015 Jul 21;12(3):396-404. PubMed PMID: 26166572; NIHMSID: NIHMS704993; PubMed Central PMCID: PMC4525481
4. Bar-On D, Wolter S, van de Linde S, Heilemann M, Nudelman G, Nachliel E, Gutman M, Sauer M, **Ashery U**. Super-resolution imaging reveals the internal architecture of nano-sized syntaxin clusters. J Biol Chem. 2012 Aug 3;287(32):27158-67. PubMed PMID: 22700970; PubMed Central PMCID: PMC3411058.
5. Bielopolski N, Lam AD, Bar-On D, Sauer M, Stuenkel EL, **Ashery U**. Differential interaction of tomosyn with syntaxin and SNAP25 depends on domains in the WD40 β-propeller core and determines its inhibitory activity. J Biol Chem. 2014 Jun 13;289(24):17087-99. PubMed PMID: 24782308; PubMed Central PMCID: PMC4059150.
6. Perets N, Betzer O, Shapira R, Brenstein S, Angel A, Sadan T, **Ashery U**, Popovtzer R, Offen D. Golden Exosomes Selectively Target Brain Pathologies in Neurodegenerative and Neurodevelopmental Disorders. Nano Lett. 2019 Feb 27. doi: 10.1021/acs.nanolett.8b04148.
7. Wegrzynowicz M, Bar-On D, Calo’ L, Anichtchik O, Iovino M, Xia J, Ryazanov S, Leonov A, Giese A, Dalley JW, Griesinger C, **Ashery U**, Spillantini MG. Depopulation of dense α-synuclein aggregates is associated with rescue of dopamine neuron dysfunction and death in a new Parkinson’s disease model. Acta Neuropathol. 2019;138(4):575-595. doi:10.1007/s00401-019-02023-x
8. Lavi A, Sheinin A, Shapira R, Zelmanoff D, Ashery U. DOC2B and Munc13-1 differentially regulate neuronal network activity. Cereb Cortex. 2014 Sep;24(9):2309-23. PubMed PMID: 23537531; PubMed Central PMCID: PMC4128701.
9. Shapira R, Solomon B, Efrati S, Frenkel D, **Ashery U**. Hyperbaric oxygen therapy ameliorates pathophysiology of 3xTg-AD mouse model by attenuating neuroinflammation. Neurobiol Aging. 2018 Feb;62:105-119. doi: 10.1016/j.neurobiolaging.2017.10.007. Epub 2017 Oct 20. PubMed PMID: 29141186.
10. Shapira R, Gdalyahu A., Gottfried I., Sasson E., Hadanny A., Efrati S, Blindeer P., **Ashery U**. Hyperbaric oxygen therapy alleviates vascular dysfunction and amyloid burden in an Alzheimer’s disease mouse model and in elderly patients. Aging (Albany. NY). 2021, 13, 20935–20961, doi:10.18632/aging.203485.
11. Gottfried I, Schottlender N, **Ashery U.** Hyperbaric Oxygen Treatment-From Mechanisms to Cognitive Improvement. Biomolecules. 2021 Oct 15;11(10). doi: 10.3390/biom11101520. Review. PubMed PMID: 34680155; PubMed Central PMCID: PMC8533945.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/

D. Research Support

Ongoing Research Projects

Israeli Academy of Sciences, ISF 2141/20: (Ashery PI) 15% effort support 10/01/20-09/01/25
No overlap with the current project.

Koret Foundation: (Ashery Co-PI in a Consortium) 10% effort support 10/01/19-09/01/24
No overlap with the current project.

Teva Pharmaceutics (Ashery Co-PI, Ben Maoz Co-PI) 5% effort support 10/01/20-09/30/22
No overlap with the current project.

NAME Ben Meir Maoz	POSITION TITLE Senior lecture Biomedical Engineering and Adjunct Senior lecture in Sagol School of Neuroscience, Tel Aviv University		
WEBSITE https://www.maozlab.com/			
INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Tel Aviv University, School of Chemistry, Tel Aviv, Israel	B.Sc.	07/08	Chemistry
Tel Aviv University, School of Chemistry, Tel Aviv, Israel	M.Sc.	07/10	Chemistry
Tel Aviv University, School of Chemistry, Tel Aviv, Israel	Ph.D.	07/13	Chemistry
Harvard University, MA, USA	Post-doc	08/18	Biomedical Engineering
Harvard University, MA, USA	Mini-MBA	08/18	MBA

A. Personal Statement

Our laboratory works developing sophisticated *in vitro* human model which better mimic the *in vivo* micro-environment and functionality, using Organs-on-a-Chip. This include developing and integrating sophisticated sensors in the Organ-on-a-Chip platform to allow *in situ* measurements of the cellular electrophysiology, metabolism, secretome and other vital parameters. While our lab specializes in the peripheral and central nerves systems, and created a metabolicly couple model of the human neurovascular unit, we are also developing high throughput platform for linking up to 7 human Organ-on-a-Chip, to allow high throughput drug and toxicant screening. Lastly, we specialize in the biotic-abiotic interface.

B. Positions and Honors

- 2022 Organizing committee ISSCR
- 2022 Editorial board Stem-cell reports
- 2021 Promising 40 under 40 in "The Marker"
- 2020 ERC grant
- 2018 Azrieli Fellowship for Academic Excellence and Leadership
- 2016-2018 Harvard-Wyss Technology Development Fellowship

C. Selected Peer-reviewed Publications

H-Index: 21 Citations: 2526 https://scholar.google.com/citations?user=-6wwx7gAAAAJ&hl=en

Highlighted papers:

1. R. Rauti, A. Ess, B. Le Roi, Y. Kreinin, M. Epshtein, N. Korin, B. M. Maoz; "Transforming a Well into a Chip: A Modular 3D-Printed Microfluidic Chip" **APL bioengineering** 5.2 **2021**: 026103
2. N. Renous, M.D. Kiri, R.A. Barnea, R. Rauti, Y. Leichtmann-Bardoogo,& B.M. Maoz, "Spatial trans-epithelial electrical resistance (S-TEER) integrated in organs-on-chips". **Lab on a Chip**. 2022
3. A. Herland*, B. M. Maoz*, et al."Quantitative prediction of human drug pharmacokinetic responses enabled by fluidically coupled vascularized organ chips", **Nature Biomedical Engineering**, **2020**
4. R. Novak*, M. Ingram*, S. Clauson*, D. Das*, A. Delahanty*, A. Herland*, B.M. Maoz*, et al. "Robotic incubator insert platform for human body-on-chips experimentation"; **Nature Biomedical Engineering**, **2020**
5. B. M. Maoz*, A. Herland*, et al. "A linked organ-on-chip model of the human neurovascular unit reveals the metabolic coupling of endothelial and neuronal cells;" **Nature Biotechnology, 2018**

D. Research Support

1. Developing advance *in* vitro model of the neurovascular unit
2. Transforming a well into a-Chip
3. Integrating sensors in advance *in* vitro model
4. Linking multiple Organs-on-a-Chip

The Blavatnik School of Computer Science
The Sackler Faculty of Exact Sciences
Tel Aviv University

March 6, 2022

Dear Colleagues:

I write as the head of the Blavatnik School of Computer Science in strong support of the proposal entitled *An integrated engineering-computational-biological (ECB) approach to unravel molecular dysfunction in Parkinson's disease*.

I strongly support and endorse Prof. Sharan and believe in his ability of accomplishing the proposal.

Sincerely,

Sivan A. Toledo

Professor
Head of the Blavatnik School of Computer Science

Iby and Aladar Fleischman
Faculty of Engineering
Department of Biomedical Engineering

TEL AVIV UNIVERSITY
אוניברסיטת תל אביב

הפקולטה להנדסה
ע"ש איבי ואלדר פליישמן
המחלקה להנדסה ביורפואית

05.03.22

Support letter for Dr. Ben M. Maoz

It is with great pleasure, I endorse Dr. Ben Maoz from our department (Biomedical Engineering) for submitting his proposal titled: *An integrated engineering-computational-biological (ECB) approach to unravel molecular dysfunction in Parkinson's disease.*
Dr. Maoz has all the necessary tools for succeeding and accomplishing this proposal.

Prof. Nati Shaked
Chair of the Department of the Biomedical Engineering

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