Name: Andrea Szuchman-Sapir **Date: June 2024**

CURRICULUM VITAE

1. Personal Details

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2. Higher Education

A. Undergraduate and Graduate Studies

Period of Study	Name of Institution and Department	Degree	Year of Approval of Degree
1991-1994	Haifa University, Oranim College, Department of Biology	B.Sc.	1994
1996-2000	Ben-Gurion University of the Negev, Department of Life-Sciences.	M.Sc.	2000
2001-2006	Technion, Faculty of Medicine	Ph.D.	2006

B. Post-Doctoral Studies

Period of Study	Name of Institution, Department and Host	Degree	Year of Completion
2006-2009	Vascular Biology Group, ANZAC Research Institute, Concord Hospital, NSW. Australia. Host: Dr. Paul Witting.	Post-Doctoral	2009

	In collaboration with The Heart Research Institute Sydney, Australia. Host: Prof. Michael Davies.		

3. Academic Ranks and Tenure in Institutes of Higher Education

Dates	Name of Institution and Department	Rank/Position
2006-2009	Vascular Biology, ANZAC Research Institute, Concord Hospital, NSW. In collaboration with The Heart Research Institute Ltd, Sydney, Australia.	Post-Doctoral
2009-2011	Tel-Hai College	Adjunct teacher
2009-2016	MIGAL Research Institute	Associate researcher at the Nutrition and Human Health Laboratory
Since 2011	Tel-Hai College	Faculty member
*Since 2016	Tel-Hai College	Senior lecturer
*Since 2016	MIGAL Research Institute	Head of the Vascular Signaling research group
Since 2021	Tel-Hai College	Tenure track

4. Offices in Academic Administration

Dates	Name of Institution	Role
Since 2011	Tel-Hai College and MIGAL Research Institute	Supervision of 14 M.Sc students, 1 PhD student (Co-supervising at the Bal-Ilan Institute), and 4 Post-doc students.
*2017-2021	Tel-Hai College	Chairman of the Institutional Review Board (IRB) for human subject research.
*Since 2019	Tel-Hai College	Reviewing & examining M.Sc. Thesis and Research projects in the Biotechnology and Nutrition departments
*2021	Tel Hai College	Examining Internal grants

*Since 2021	Tel-Hai College	Head of the Life-science Faculty Institutional Review Board
*2021-2024	Tel-Hai College	Member of the Gender Equity Unit
*Since 2023	MIGAL Research Institute	Head of the Nutrition and Natural Compound department
*Since 2023	MIGAL Research Institute	Member of the Scientific Board and the Ph.D. committee
*2023-2027	Tel-Hai College	Head of the Nutrition Sciences M.Sc. program

5. Scholarly Positions and Activities outside the Institution

A. Activities outside the Institution

Year	Name of Institution	Role
2013-2016	The Israeli Society for Oxygen and Free Radical Research	Treasurer
*2019	Hebrew University of Jerusalem	Examining Ph.D. thesis
*2021	Dead Sea & Arava Science Development	Reviewing Tenure track position for the Scientific Committee
*Since 2022	Israeli Society for Research, Prevention and Treatment of Atherosclerosis	Member of the scientific board
*2022	The U.S.-Israel Binational Science Foundation (BSF)	Reviewing proposal
*2022	Frontiers in Pharmacology journal.	Reviewing articles

B. Membership in professional organizations

Date	Organization Name
2007	Australian Atherosclerosis Society
2008	The Society of Free Radical Research (Australasia).
Since 2010	The Israeli Society for Research, Prevention and Treatment of Atherosclerosis.
2013-2016	The Israeli Society for Free Radicals Research.
*2020	The Society for Redox Biology and Medicine.

*2022	The Israeli Society for Free Radicals Research

6. Participation in Scholarly Conferences

A. Active Participation

Date	Name of Conference	Place of Conference	Role
2007	The annual Australian Atherosclerosis Society meeting	Fremantle, Australia.	**Oral presentation**
2008	The Society of Free Radical Research (Australasia) Annual Meeting	Melbourne, Australia.	**Oral presentation**
2008	The 15th International Vascular Biology Meeting.	Sydney, Australia	Poster presentation
2010	The 15th Annual Meeting of the Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Eilat, Israel	**Oral presentation**
2011	4th Symposium International Nutrition, Biologie de l'Oxygene et Medecine.	Paris, France.	Poster presentation
2012	The 16th Annual Meeting of the Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Eilat, Israel	Poster presentation
2013	The 17th Annual Meeting of the Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Eilat, Israel	**Oral presentation**
2014	Endothelial Cell Phenotypes in Health & Disease. Gordon Research Conference.	Girona, Spain.	Poster presentation
2014	The spring meeting of the Israeli Society for Hypertension.	Haifa, Israel.	**Invited speaker**
2015	Bioactive Lipids Conference.	Budapest, Hungary.	**Oral presentation**
2015	The 18th Annual Meeting of The Israeli Society for Research,	Tel-Aviv, Israel.	**Invited chairman & Oral presentation.**

	Prevention and Treatment of Atherosclerosis.		
*2016	The 6th European Workshop on Lipid Mediators (EWLM)	Frankfurt, Germany.	Poster presentation
*2016	The 21th Annual Meeting of The Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Haifa, Israel.	**Invited speaker**
*2017	ESM-EVBO Joint meeting	Geneva, Switzerland	Poster presentation
*2017	ILANIT/FISEB conference.	Eilat, Israel.	**Invited speaker**
*2017	The 22th Annual Meeting of The Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Zikhron Yaakov, Israel	**Invited speaker**
*2018	International Vascular Biology and Medicine (IVBM)	Helsinki, Finland	Poster presentation
*2018	The spring meeting of the Israeli Society for Hypertension.	Jerusalem, Israel.	**Invited speaker**
*2019	European Atherosclerosis Society (EAS)	Maastricht, Netherlands.	**Oral presentation** (e-poster)
*2019	The 24th Annual Meeting of The Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Caesarea, Israel.	**Invited speaker**
*2020	Society for Redox Biology and Medicine annual conference.	Virtual conference.	**Oral presentation**
*2021	The 25th Annual Meeting of The Israeli Society for Research, Prevention and Treatment of Atherosclerosis.	Kfar Blum, Israel.	**Invited chairman.**
*2021	Horizons in Vascular Biology.	Bar-Ilan, Zefat.	**Invited speaker**
*2022	The 8th European Workshop on Lipid Mediators.	Stockholm, Sweden	**Oral presentation**

*2022	The Israel Society for Oxygen and Free Radical Research.	Tel Aviv University.	**Invited speaker**
*2023	European Atherosclerosis Society (EAS).	Manheim, Germany.	**Oral presentation** (e-poster)
*2023	ILANIT conference.	Eilat Israel.	**Invited speaker**
*2023	Research seminar	Western Galilee Medical Center	**Invited speaker**
*2024	Research seminar	LBI, Medical University of Graz, Austria	**Invited speaker**

B. **<u>Organization of Conferences or Sessions</u>**

Date	**Name of Conference**	**Place of Conference**	**Role**
2013	The 29th conference of the Israeli Society for Free Radicals Research.	Tel-Hai.	Organization of the conference's administrative and academic
2014	The 30th conference of the Israeli Society for Free Radicals Research.	Bar-Ilan University.	Organization of the conference's administrative and academic
*2022	ILANIT session of the Israeli Society for Research, Prevention, and Treatment of Atherosclerosis	Eilat.	Introducing the association to the membership of the associations included in the Ilanit conference and helping with the organization of the meeting
*2023	The 27th annual meeting of the Israeli Society for Research, Prevention, and Treatment of Atherosclerosis.	Dead sea.	Recruiting lecturers and reviewing the abstracts as part of the conference's scientific committee.

7. Research Grants

A. Grants Awarded

Role in Research	Co-Researchers	Topic	Funded by/ Amount	Year
PI		Novel pathway for blood pressure regulation involves paraoxonase 1 and epoxygenase arachidonic acid metabolites.	The Israeli Society for Research, Prevention and Treatment of Atherosclerosis. Research award 7500$	2012-2013
PI		Novel pathway for blood pressure regulation involving paraoxonase 1 and epoxygenase arachidonic acid metabolites.	ISF- Israel Science Foundation research fellowship (#834/12, for 3 years, 578K ILS).	2012-2015
PI		The regulation of 5,6-DHTL, a new endothelial-derived hyperpolarizing factor, by paraoxonase 1 in the modulation of vascular tone.	ISF- Israel Science Foundation research fellowship (1323/15, for 3 years, 600K ILS).	2015-2018
*PI	Prof. Gutterman David, Medical College of Wisconsin, Milwaukee, USA.	PON1 regulates blood pressure via EDHF.	BSF- start-up grant. (#2015254, 60K $ for 2 years).	2016-2018
*PI	Prof. Shaul Atar, Galilee Medical Center, Nahariya.	Arterial dilating activity of an EPA metabolite, a novel endothelial-derived hyperpolarizing factor (EDHF), as an anti-hypertensive drug candidate.	Israel Innovation Authority. (1320K ILS for 2 years).	2018-2020
*PI	Prof. Shaul Atar, Galilee Medical Center, Nahariya.	Arterial dilating activity of an EPA metabolite, a novel endothelial-derived hyperpolarizing factor (EDHF), as an anti-hypertensive drug candidate.	Third-year continuation of the Kamin project from the Israel Innovation Authority. (700K ILS).	2021-2022

A.1. Internal grants

Role in Research	Co-Researchers	Topic	Funded by/ Amount	Year
*PI		Molecular regulation of endothelial and vascular dysfunction by lactones derived from polyunsaturated fatty acids	Migal internal grant. (80K ILS).	2020
*PI		Harnessing the computational power of genomics and computational biology to understand the mechanisms underlying dietary-induced arteriosclerosis, NAFLD, and the mechanisms of action for reducing hypertension.	Migal-genomics and computational biology requests of resources (8K ILS)	2021
*Co-PI	PI-Dr. Sanaa Musa	Nitric Oxide donors-based cannabinoid skeleton as a privileged scaffold for bifunctional therapeutic molecules.	Tel-Hai internal grant (40K ILS).	2022-2023
*Co-PI	PI- Dr. Faiga Magzal Co-PI- Dr. Roee Gutman Co-PI- Prof. Soliman Khatib	Does ultra-processed food, developed for mitigating food security challenges and climate change, affect metabolic and health outcomes? A pre-clinical study.	MIGAL internal grant. (200K ILS).	2024-2026

B. Submission of Research Proposals – Pending

Role in Research	Co-Researchers	Topic	Funded by	Year
*PI		Bioactive lactone oxylipins mechanism of action in microvascular dysfunction: From genomic interrogation to	ISF	2024-2029

		in-vivo regulation		
*Co-PI	PI-Faga Magzal, Co-PI-Roee Gutman, Co-PI- Soliman Khatib	Impact of Food Processing on Metabolic Health and the Gut-Brain Axis.	Ministry of Science. (The first stage was accepted).	2024-2027
*Co-PI	A consortium of five academic institutes in Israel (BGU, TAU, THC, HUJ, Ariel Uni.)	Programme to support research hubs in the areas of food system and sustainable nutrition	Vatat	2025-2028

C. <u>Submission of Research Proposals – Not Funded</u>

Role in Research	Co-Researchers	Topic	Funded by	Year	Score
*Co-PI	PI-Dr. Elena Slutzky Smith Co-PI- Dr. Camille Oger University of Montpellier, France Co-PI- Dr. Luca Meoli, Charité, Institute of Clinical Physiology & Center for Cardiovascular Research, Berlin, Germany	Novel Oxidized PUFA Metabolites for the Treatment of Hypertension: Discovery, Library Compilation, and Investigation of Mechanism	ERA-CVD	2019	
*Co-PI	PI Prof. Shaul Atar	The Effect of hypertension and anti-hypertensive drugs efficacy on endothelial ion channels	המשרד לפיתוח הפריפריה הנגב והגליל	2019	

		expression in 5/6 nephrectomy rat model.			
*PI	Co-PI- Dr. Offir Ertracht Cardiovascular Research Laboratory, Galilee Medical Center, Nahariya	The effect of the ACE2-SARS-CoV-2 interaction on vascular reactivity mechanisms and blood pressure	ISF-Kill Corona	2021	
*PI		Molecular regulation of endothelial and vascular dysfunction by lipid lactone mediators	ISF	2022	
*Co-PI	PI-Dr. Sanaa Musa	Nitric Oxide donors based cannabinoid skeleton as a privileged scaffold for bifunctional therapeutic molecule	Ministry of Sciences	2023	
*PI	Co-PI- Prof. Netanel Korin, Thechnion	PUFA-lactones vascular-targeted nanocarrier for improving vasodilation in microvascular dysfunction	Ministry of Sciences	2023	
*Coordinator	PI- Dr. Slaven Crnkovic Medical University of Graz, Austria PI- Dr. Baiba Vilne Rīga Stradiņš University, Latvia PI- Dr. Florence Pinet INSERM-RANCE PI-Prof. Irene M Lang Medical University of Vienna, Austria	REBALANCE- Restoring vascular function in pulmonary hypertension by PUFA lactones	ERA4Health Joint Transnational Call for Proposals	2023	Reached to the final stage

8. Scholarships, Awards and Prizes

Year	Award	Institute
2009-2011	Grant for Returning Scientist.	The Center for Absorption in Science, Israel.
2010	Excellence-in-teaching award	Tel-Hai College.
*2017	Excellence-in-teaching award	Tel-Hai College.

9. Teaching

A. Courses Taught in Recent Years

Year	Name of Course	Type of Course	Degree	Number of Students
2009-2021	General Chemistry	Introduction Course	B.Sc level	100
Since 2010	Human Nutrition	Course	B.Sc level	70
2010-2013	Biochemistry	Laboratory	B.Sc level	30
Since 2011	Principles in Human Nutrition	Course	B.Sc level	30
Since 2012	Seminar in Nutrition	Seminar Course	B.Sc level	20
2013-2017	Seminar in Biotechnology	Seminar Course	B.Sc level	20
2021-2011	Lipids metabolism in health and disease	Course	M.Sc level	6

10. Supervision of Graduate Students

Name of Student	Title of Thesis	Degree	Date of Completion /in Progress
Eryanni Suzy	5,6-δ-DHTL, a stable metabolite of arachidonic acid, as a potential substrate for paraoxonase 1	M.Sc	2013
Levy Reut	5,6 –DHTL-dependent endothelial hyperpolarization mechanism regulated by PON-1.	M.Sc	2014

Otmazgin Ziv (Co-PI- Prof. Snait Tamir)	Paraoxonase1 effect on blood pressure regulation.	M.Sc	2015
Gilad Dan	The effect of Paraoxonase1 on 5,6-δ-DHTL - dependent vascular dilation.	M.Sc	2016
*Magzal Faiga (Bar-Ilan University, PI- Prof. Kristal Batya)	Post-translational modifications of albumin as a pro-inflammatory agent in hypoalbuminemia	Ph.D.	2016
*Atiya Shahar	The effect of Paraoxonase – 1 structure and activity on 5,6-δ-DHTL-mediated calcium elevation in endothelial cells	M.Sc	2017
*Pinhas Shaily	The Effect of Paraoxonase 1 Enzyme on Endothelial Cells Hyperpolarization Mediated by EPA-Lactone and DHA-Lactone	M.Sc	2019
*Ben-David Raz	Investigation of paraoxonase-1 endocytosis and activity in endothelial cells	M.Sc	2019
*Amram Eitan	The effect EPA-L hydrolysis by PON-1 on endothelial-dependent vascular dilation	Post-Doctoral	2019
*Bar-Sheshet Michal	Investigation of the vasodilation and blood pressure lowering effect mediated by EPA-metabolite in 5/6 nephrectomy hypertensive rat model	M.Sc	2020
*Boginya Alexandra	The effect of PUFA-lactones on ion flux in endothelial cells	Post-Doctoral	2020
*Slutsky-Smith Elana	Fishing for lipid lactones using selective reaction and characteristic fragmentation pattern	Post-Doctoral	2021
*Asulin Meitar	The effect of lactones from polyunsaturated fatty acid on the hyperpolarization mechanisms in endothelial cells	M.Sc	2022
*Dhananjayan Karthik	EPA-Lactone derivative mechanism of action in pulmonary arterial hypertension rat model	Post-Doctoral	2024

*Gorodetzer Nadav	Investigation of the potential receptors through which PUFA-lactone molecules act in endothelial cells	M.Sc	In progress (thesis has been submitted)
*Cohen Zohar	Nanoencapsulated PUFA-lactones for the treatment of endothelial dysfunction	M.Sc	In progress (second year)
*Chudonovsky Michal	Mechanisms and pathways of EPA-Lactone in endothelial cells in pulmonary hypertension	M.Sc	In progress (first year)
*Yosef Shoval (PI- Dr. Idan Perman)	Neurotrophic potential and gene expression pathways activated by secondary metabolites derived from Hericium erinaceus and Psilocybe cubensis mushrooms.	M.Sc	In progress (first year)

11. Miscellaneous

2020- During the COVID-19 pandemic, the post-doctoral period of Boginya, Alexandra was shortened.

2023- During the war, the post-doctoral period of Dhananjayan Karthik was shortened.

12. Professional Experience

Since 2011 Supervision of school students in their biotechnology project.

Since 2011 Active scientists at the "Researchers-Night"; "Scientist at Kinder Garden", Kiryat Shmona, and in Kibbutz Malkiya. Ministry of Science.

PUBLICATIONS

A. Ph.D. Dissertation

"Characterization of oxidative stress by synthesized exogenous markers". Supervised by Prof. Michael Aviram and Prof. Jacob Vaya. Dec 2005. Approved by the Senate, Technion, Israel.

B. Scientific Books (Refereed)

Edited Books and Special Journal Issues - Accepted for Publication

Dhananjayan K and **Szuchman-Sapir A**. 2024. Recent advances in oxylipin-driven repair mechanisms in vascular dysfunction-related diseases. In "Studies in Natural Products Chemistry" (Bioactive Natural Products), edited by Prof. Atta-ur-Rahman, FRS, Elsevier Science Publishers, The Netherlands. Accepted for publication.

C. Articles in Refereed Journals

Published

1. **Szuchman A**, Aviram M, Tamir S, Vaya J. 2003. Cholesterol, linoleic acid or/and tyrosine yields different spectra of products when oxidized alone or in a mixture: studies in various oxidative systems. *Free Radic Res.* 37: 1277-88. IF-2.99, Q2, HI-13.
2. **Szuchman A**, Aviram M, Soliman K, Tamir S, Vaya J. 2006. Exogenous tyrosine-linoleate marker as a tool for the characterization of cellular oxidative stress in macrophage. *Free Radic Res*. 40: 41-52. IF-2.99, Q2, HI-19.
3. **Szuchman A**, Aviram M, Musa R, Soliman K, Vaya J. 2008. Characterization of oxidative stress in blood from diabetic versus hypercholesterolemic patients, using a novel synthesized marker. *Biomarkers.* 30: 1-13. IF-2.52, Q2, HI-41.
4. Witting P, Zeng B, Wong M, McMahon AC, Rayner BS, **Sapir AJ**, Lowe HC, Freedman SB, Brieger DB. 2008. Polymorphonuclear leukocyte phagocytic function increases in plasminogen knockout mice. *Tromb Res.* Apr 122: 674-82. IF-2.45, Q2, HI-9.
5. **Szuchman-Sapir A**, Pattison DI, Ellis NA, Hawkins CL, Davies MJ, Witting PK. 2008. Hypochlorous acid oxidizes methionine and tryptophan residues in myoglobin. *FRBM*. 45: 789-98. IF-5.85, Q1, HI-41.
6. **Szuchman-Sapir A**, Pattison DI, Davies MJ, Witting PK. 2010. Site –specific hypochlorous acid-induced oxidation of recombinant human myoglobin affects specific amino acid residues and the rate of cytochrome b_5-mediated heme reduction. *FRBM.* 48: 35-46. IF-5.85, Q1, HI-17.
7. Yehuda I, Madar Z, **Szuchman-Sapir A**, Tamir S. 2011. Glabridin, a phytoestrogen from licorice root, up-regulates the intracellular antioxidant defense mechanism under glucose stress. *Phytother Res.* May 25: 659-67. IF-2.66, Q2, HI-42.
8. Vaya J, **Szuchman** A, Tavori H, Aluf Y. 2011. Oxysterols formation as a reflection of biochemical pathways: summary of in-vitro and in-vivo studies. *Chem Phys Lipids*.164: 438-42. IF-2.69, Q3, HI-27.
9. Yehuda H, **Szuchman-Sapir** A, Khatib S, Tamir S. 2011. Human atherosclerotic plaque lipid extract promotes expression of proinflammatory factors in human monocytes and macrophage-like cells. *Atherosclerosis.* 218: 339-43. IF-4.01, Q1, HI-31.
10. **Szuchman-Sapir A,** Etzman M, Tamir S. 2012. Human atherosclerotic plaque lipids impair cellular antioxidant enzymes while enhancing ROS production in monocytes. *BBRC.* 423:884-8. IF-2.38, Q2, HI-12.
11. **Szuchman-Sapir A**. 2014. Endothelial-derived hyperpolarizing factors (EDHF) and blood pressure regulation – mechanism of action. Review. Israeli Bilingual Journal of Hypertension.

12. Eryanni S, Khatib S, Levi-Rosenzvig R, Tamir S**, Szuchman-Sapir A**. 2015. 5,6 –δ-DHTL, a stable isomer of arachidonic acid, is a potential substrate for paraoxonase 1. *BBA - Molecular and Cell Biology of Lipids* 1851:1118-1122. IF-4.90, Q1, HI-28.
13. *Yehuda I, Madar Z, Leikin-Frenkel A, **Szuchman-Sapir A**, Magzal F, Markman G, Tamir S. 2016. Glabridin, an isoflavan from licorice root, upregulates paraoxonase 2 expression under hyperglycemia and protects it from oxidation. *Molecular Nutrition & Food Research***.** 60(2):287-99. IF-4.3, Q1, HI- 39.
14. *Wang XS , Kim HB , **Szuchman-Sapir A** , McMahon A , Dennis JM , Witting PK. 2016. Neutrophils recruited to the myocardium after acute experimental myocardial infarct generate hypochlorous acid that oxidizes cardiac myoglobin. *Archives of Biochemistry and Biophysics.* 612:103-114. IF-3.16, Q2, HI-24.
15. *Levi-Rosenzvig R, Beyer AB, Hockenberry J, Shelly Ben-Shushan R, Chuyun D, Atiya S, Tamir S, Gutterman DD, **Szuchman-Sapir A**. 2017. 5,6-δ-DHTL, a stable metabolite of arachidonic acid, is a potential EDHF that mediates microvascular dilation. *FRBM.* 103:87–94. IF-5.6, Q1, HI-17.
16. *Magzal F, Sela S, **Szuchman-Sapir A**, Tamir S, Michelis R, Kristal B. 2017. In-vivo oxidized albumin– a pro-inflammatory agent in hypoalbuminemia. *PLoS One. 24:1-14.* IF-2.8, Q1, HI-36.
17. *Gilad D, Atiya S, Mozes-Autmazgin Z, Shelly Ben-Shushan R, Ben-David R, Amram E, Tamir S, Chuyun D, and **Szuchman-Sapir A.** 2019. Paraoxonase 1 in endothelial cells impairs vasodilation induced by arachidonic acid lactone metabolite. *Biochim Biophys Acta Mol Cell Biol Lipids. 17;1864(3):386-393.*IF-4.4, Q1, HI-16.
18. *Ben-David R, Chuyun D, **Szuchman-Sapir A**. 2020 The uptake mechanism and intracellular fate of Paraoxonase-1 in endothelial cells. *Free Radic Biol Med. 31* (20), 30487-1. IF- 5.65, Q1, HI-5.
19. *Barsheshet M, Ertracht O, Boginya A, Reuveni T, Shaul A, **Szuchman-Sapir A**. 2021 Vasodilation and blood pressure-lowering effect mediated by 5,6-EEQ lactone in 5/6 nephrectomy hypertensive rats. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, 1866(12):159031. IF-4.69, Q1, HI-2.
20. *Slutsky Smith EA, Khatib S, **Szuchman-Sapir A**. 2022 Fishing for lipid lactones using selective reaction and characteristic fragmentation pattern. *Journal of Chromatography B*, 1197:123201. IF-3.3, Q2, HI-1
21. *Pinhas S, Amram E, Slutsky-Smith E, Ertracht O, Atar S, Chuyun D, **Szuchman-Sapir A.** 2022 Paraoxonase 1 hydrolysis of EPA-derived lactone impairs endothelial-mediated vasodilation. Prostaglandins and Other Lipid Mediators. *Prostaglandins and Other Lipid Mediators* 162: 106665. IF-3.2. Q2, HI-1.
22. *Asulin M, Gorodetzer N, Fridman R, Shelly Ben-Shushan R, Cohen Z, Beyer A M, Chuyun D, Gutterman D D, **Szuchman-Sapir A**. 2024 5,6-diHETE lactone (EPA-L) mediates hypertensive microvascular dilation by activating the endothelial GPR-PLC-IP3 signaling pathway. *Biochemical and Biophysical Research Communications.* 700:149585. IF-3.1. Q1.

In preparation

23. *Dhananjayan K, Ertracht O, Atar S, and **Szuchman-Sapir Andrea.** 2024. EPA-Lactone derivative, 5,6-diHETE lactone, improves pulmonary arterial hypertension in MCT- rat model.

D. Patent

*Title: "EPA-lactone for treatment of microvascular dysfunction"
Inventors: Andrea SZUCHMAN-SAPIR
Patent Application in the European Union (EP3976047A4) and in the United States (US20220241233A1).

In the name of Gavish-Galilee Bio Applications Ltd. Ref.: GAVISH-118 PCT

https://patents.google.com/patent/WO2020245816A1/en?inventor=andrea+sapir

E. Summary of my Activities and Future Plans

The research conducted during my doctoral studies at the Technion Rappaport Institute of Medicine has sparked my enthusiasm for delving into the field of human vascular biology. My motivation stems from the desire to explore the fundamental chemical and biological mechanisms that govern and impact human health, with potential implications in medicine. For over 18 years, I have been engaged in diverse research studies studying the signaling molecules that influence the cardiovascular system in both health and disease states. Specifically, my attention has been directed toward elucidating the cause and effects of diverse oxidative alterations in lipids and proteins associated with conditions such as atherosclerosis, diabetes, and myocardial infarction. I focused on the role of oxylipins in microvascular dysfunction-related disorders like pulmonary hypertension, investigating their chemical formation and the biological pathways regulating their signaling within cells and blood vessels. The expertise and insights acquired through my experiences in Israel and abroad have broadened the scope of my research, leading to publications and patents that contribute to understanding the underlying pathways involved in these pathological conditions.

Publications and Contribution to Science

*Numbers in superscript relate to the publication number in my CV

During my Ph.D., I studied cellular redox chemistry by developing a novel synthetic marker for oxidative stress. This marker provides information on oxidative stress presence, extent, and metabolic consequences in biological systems. Using this marker, it was demonstrated that different patterns of oxidation products are produced by cholesterol, linoleic acid (LA), and tyrosine (Tyr) when exposed to various ROS separately or in mixtures[1]. Then, new markers composed of these molecules were synthesized to detect and characterize oxidative stress (OS) outcomes. The marker, N-linoleoyl tyrosine (N-LT), was oxidized by macrophages from atherosclerotic mice to yield N-LT-hydroperoxide (N-LT-OOH) at higher levels than control mice, suggesting it is a characteristic oxidative product of atherosclerosis[2]. Further, a triple marker, N-linoleoyl tyrosine cholesteryl ester (N-LT-Chol), was used to show significantly higher and specific oxidation levels in diabetic patients compared to controls. Consumption of pomegranate juice significantly reduced N-LT-Chol oxidation[3]. These molecules provided insights into oxidative stress in various pathological conditions[8].

During my post-doctoral period at the Vascular Biology Group, ANZAC Research Institute, I studied oxidative stress in myocardial infarction by investigating myoglobin's post-translational modifications. These studies, involved *in vitro* and *in vivo* models, characterized oxidative modifications of myoglobin and explored its role in inflammation post-myocardial infarction. Analytical methods for identifying peptide-specific modifications of myoglobin using LC/MS were established in collaboration with the Bioanalytical Mass Spectrometry Facilities at NSW University. These studies have been published in peer-reviewed journals[4,5,6,14] and presented at three national and international conferences.

On my return, I joined the Human Health and Nutrition Sciences Laboratory at the MIGAL Research Institute as a research fellow. As a returning scientist, I was awarded a fellowship by The Center for Absorption in Science. During this period, I established research projects, trained students during

their M.Sc. and Ph.D. research, and taught B.Sc.-level courses at Tel-Hai College. Scientifically, I was extensively involved in studies that focused on the cellular antioxidant system during atherosclerosis and diabetes and the effect of the phytoestrogen Glabridin in these processes. These studies revealed the effect of the human atherosclerotic plaque lipid extract on inflammation and the antioxidant system in monocytes and macrophages[7,9,10,13]. My experience in protein modification analyses using mass spectrometry was the basis for collaborating with Prof. Kristal at the Western-Galilee Medical Center. In this study, it was shown that oxidative modifications of human serum albumin (HSA) reflect the severity of oxidative stress in chronic kidney disease (CKD) and induce endothelial inflammation at the transcriptional and translational levels[16].

As an independent researcher, I received an ISF research fellowship and a fellowship from The Israeli Society for Research, Prevention, and Treatment of Atherosclerosis, which enabled me to launch my scientific path. My research focused on a novel blood pressure-regulating pathway involving CYP450 pathway metabolites and the Paraoxonase 1 (PON1) enzyme. We determined the kinetic formation and hydrolysis of 5,6-DHTL by PON1, showing its significant impact on blood pressure regulation[12]. We found that PON1 endocytosis is mediated by a dynamin-dependent mechanism and directed to lysosomal degradation[18], while, under endothelial dysfunction, PON1 internalization increases, impacting microvessel dilation[21]. Utilizing a PON1 knockout mouse model, we demonstrated PON1's effect on vasodilation mediated by 5,6-δ-DHTL[17].

The following ISF Research Grant aimed to reveal the regulatory role of PUFA-lactone metabolites. We discovered novel vascular dilators from Arachidonic acid and Eicosapentaenoic acid (EPA), collaborating with Prof. Gutterman to demonstrate their endothelial-dependent mechanism in human peripheral arteries[15]. Our studies showed that these oxylipins compensate for nitric oxide pathway loss in vascular dysfunction, mediating hyperpolarization through the GPCR-PL-IP3 pathway[22]. We developed a new selective reaction for fishing lipid lactones from biological samples[20]. These discoveries were summarized in a review and a book chapter[11,24].

These findings led to a patent[25] and a 3-year grant from the Israeli Innovation Authority. We established rat models for hypertension, demonstrating that EPA-derived lactone oxylipins significantly reduced blood pressure and repaired microvascular dysfunction[19,23]. A pharmaceutical company in Austria (AOP Health) expressed interest in further advancements.

In 2023, I established a European consortium to explore oxylipin lactones' involvement in human lung tissues. Despite not securing funding, the collaborative efforts continued during my sabbatical at the Medical University of Graz, Austria, which will further open new horizons to my research interests in investigating and exploring new pathways and therapeutic potential for microvascular dysfunction-related disease.

Additional qualifications include establishing the Vascular Signaling research group at MIGAL, mentoring 14 M.Sc and 4 post-doctoral students, and serving as chairman of the Tel-Hai Institutional Review Board. I contributed to advancing gender equality within academia and became the Head of the Nutrition and Natural Compound department at MIGAL. In 2023, I was appointed head of the Master of Science program in Nutrition at Tel-Hai College, aiming to enhance the NutriTech program for investigating the diet-health relationship.