BIOGRAPHICAL SKETCH

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NAME: Friedmann-Morvinski, Dinorah

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

POSITION TITLE: Associate Professor at the Department of Biochemistry and Molecular Biology, Faculty of Life Science, Tel Aviv University

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
"Escuela Integral Hebreo Uruguaya", Montevideo-Uruguay	Baccalaureate	1982-1988	Medicine
School of Life Sciences, University of the Republic of Uruguay. Montevideo-Uruguay	B.Sc.	1990-1995	Biochemistry
Hadassah University Hospital, Faculty of Medicine, Institute of Biotechnology, Jerusalem, Israel	M.Sc.	1995-1997	Biotechnology
The Weizmann Institute of Science, Department of Immunology. Rehovot-Israel	Ph.D.	2000-2005	Immunology
The Salk Institute, La Jolla, CA	Research Associate	2005-2010	Molecular Biology
The Salk Institute, La Jolla, CA	Senior Research Associate	2010-2015	Molecular Biology

A. Personal Statement

I have an immunology, molecular biology and cancer research background, the experience and qualifications that make me particularly well-suited to assume the role as PI and lead this research proposal. I had the honored to be supervised and mentored by two world renowned Professor in the fields of cancer research. I did my PhD at the Department of Immunology, the Weizmann Institute of Sciences, under the supervision of Prof. Zelig Eshhar, the pioneer of the chimeric antigen receptor (CAR) T cell immunotherapy. During my PhD studies I helped design the second generation of CARs, which added intracellular signaling domains from CD28 costimulatory receptors to provide the second signal required for full T cell activation. For my postdoctoral studies I joined the laboratory of Prof. Inder Verma at the Salk Institute, a world leader in gene therapy, where using lentiviral vectors I developed a new mouse model of glioblastoma (GBM). Using this model, I challenged the idea of adult stem cells as the sole source of tumor-initiating potential and generated much controversy in the cancer field by introducing a new concept: tumor reprogramming/plasticity. I was able to show that glioblastoma can originate from a variety of cells in the brain, including terminally differentiated cortical astrocytes and neurons. I proposed that oncogenic-induced dedifferentiation of mature cells in the brain to a stem/progenitor like state leads to heterogeneous glioma tumors. The genetically acquired plasticity of these cells allows progression and maintenance of this aggressive tumor and even formation of its own blood vessels by transdifferentiation. In 2015 I established my laboratory at Tel Aviv University and I am currently supervising 2 undergraduate students, 4 MSc students and 4 PhD students. The main research interest in my lab is to decipher the molecular and

cellular mechanisms of cancer cell plasticity and the contributions of the tumor microenvironment to this process. I believe that understanding these mechanisms and interactions will facilitate the development of strategies to attack this aggressive type of cancer. The main strategies we are exploring today in my lab are immune cell therapy (CAR T cells) and nanomedicine. I strongly believe that much more can be achieved by establishing interdisciplinary collaborations and by open discussions and frequent communications between project members.

B. Positions and Honors

Positions and Employment

1997-1999 Research Scientist in the R&D at Combact Diagnostic Systems Ltd. Hertzelia-Pituach-Israel
1999-2000 Lab Director at the Institute of Oncology, The Sheba Medical Center, Tel-Hashomer-Israel.
2000-2005 Consulting scientist at Massis Co., Israel.

Honors

1997 M.Sc. in Biotechnology with Honors
2006-08 EMBO Long Term Fellowship
2006-07 Pioneer Postdoctoral Endowment fund –fellowship award- The Salk Institute
2011 AACR-Aflac, Incorporated Scholar-in-Training award – AACR Annual Meeting
2014 Travel fellowship – 7th FISEB-ILANIT Conference
2014 AACR – Millennium Scholar-in-Training Award – AACR Annual Meeting
2015 AACR – Aflac, Scholar-in-Training Award – Advances in Brain Cancer Research
2017 Broad-ISF – Collaborative Project Award
2019 AAI Early career faculty travel grant

Other Experience and Professional Memberships

2006-2009 American Society of Cell and Gene Therapy (ASCGT)
2006-present The American Association for Cancer Research (AACR)
2006-present European Association of Cancer Research (EACR)
2005-present The EMBO fellows Network
2015-present Cancer Biology Research Center (CBRC), Tel Aviv University (board member)
2015-present Tel-Aviv University Sagol School of Neuroscience
2019-present American Association of Immunology (AAI)
2018-present Israeli Society of Gene and Cell Therapy (ISCGT) (board member)
2018-present Israeli Society of for Cancer Research (ISCR) (board member)
2020-present Society of Neuro-Oncology (SNO)

Selected Academic Activities and Appointments (last 5 years):

2022-present Member of Senate, Tel Aviv University, Israel.
2022 Organizer, Annual Meeting of the Israeli Society of Gene and Cell Therapy (ISGCT).
2022 Co-organizer, Annual Meeting of the Israeli Society for Cancer Research (ISCR)
2022 Co-Organizer, Brain Tumor Poland Conference, Warsaw.
2021- Organizer, Annual Meeting of the Israeli Society of Gene and Cell Therapy (ISGCT).
2021-Co-organizer, Cancer Biology Research Center (CBRC) meeting.
2020- Organizer, Annual Meeting of the Israeli Society of Gene and Cell Therapy (ISGCT).
2020-present Co-Chair, MSc International Sagol Neuroscience Program, Tel Aviv University.
2018-present coordinator of the Young PI peer forum of the Faculty of Life Sciences, Tel Aviv University

C. Contribution to Science

1. My early publications started in the field of immunology, working on an autoimmune disease, lupus, and studying the relative contributions of clonal deletion, clonal anergy, and receptor editing to tolerance induction in autoreactive B cells and their dependence on B cell receptor affinity. Our results suggested that clonal deletion and receptor editing are interrelated mechanisms that act in concert to eliminate autoreactive B cells from the immune system, with clonal anergy maybe an intermediate step in clonal deletion. I then backcrossed a “knock-in” mouse harboring a rearranged H chain from an anti-DNA hybridoma onto the

autoimmune, lupus-prone genetic background NZB/NZW mice. In this model, I found the production of high affinity autoantibodies with a very restricted repertoire of Vk utilization and suggested that the breakdown of tolerance in these mice is associated with the preferential expansion and activation of B cell clones expressing high affinity anti-DNA H/L receptor combinations.

a. Pewzner-Jung Y, **Friedmann D**, Sonoda E, Jung S, Rajewsky K, Eilat D. “B cell Deletion, Anergy Anti-DNA Heavy Chain”. Journal of Immunology, 1998, 161: 4634-4645.
b. **Friedmann D**, Yachimovich N, Mostoslavsky G, Pewzner-Jung Y, Ben-Yehuda A, Rajewsky K, Eilat D. “Production of High Affinity Autoantibodies in Autoimmune NZB/NZW F1 Mice Targeted with an Anti-DNA Heavy Chain”. Journal of Immunology, 1999, 162: 4406-4416.

2. I found the field of immunology fascinating and decided to continue my research on this field but this time in relation to cancer, tumor immunology, cancer immunotherapy and leaving behind the B cells and starting to work with T cells. During my PhD, I conducted functional analyses of Chimeric T cell receptors for adoptive cell therapy of cancer. I generated transgenic mice with different antibody-based chimeric receptors in T cells, and proved that redirected primary T cells harboring a chimeric receptor require co-stimulation for their antigen-specific activation. These findings resulted in publications and invitations to write book chapters in the field of adoptive immunotherapy of cancer.

a. **Friedmannn-Morvinski D**, Bendavid A, Waks T, Schindler D, and Eshhar Z. "Re-directed Primary T-Cells Harboring a Chimeric Receptor Require Co-Stimulation for their Antigen-Specific Activation". Blood 2005 April; 105(8): 3087-93.
b. **Friedmannn-Morvinski D** and Eshhar Z. "Adoptive Immunotherapy of Cancer Using Effector Lymphocytes Redirected with Antibody Specificity". Cancer. Update on Cancer therapeutic I. 26 May 2006;pages 25-32.
c. **Friedmann-Morvinski D** and Eshhar Z. “Adoptive Transfer of T-Bodies: Toward an Effective Cancer Immunotherapy”. J. Lustgarten et al. (eds), Targeted Cancer Immune Therapy, DOI 10.1007/978-1-4419-0170-5_16, Springer Science+Business Media, LLC 2009.

3. During my postdoctoral training, I challenged myself into a completely new field of tumor biology and lentiviral vectors. I designed a novel mouse model of glioblastoma (GBM) using inducible lentiviral vectors. Using this state-of-the-art GBM mouse model, I showed for the first time that neurons can be the cell of origin of gliomas. Furthermore, I found that any cell in the brain can be the target of genetic alterations that can lead to gliomagenesis. We proposed that if a mature/differentiated cell is transformed, it acquires the capacity to reprogram (or dedifferentiate) to a more progenitor/stem cell state, which can then not only maintain its pluripotency, but also give rise to the heterogeneous cell populations observed in high-grade gliomas, including endothelial cells to form new blood vessels. We termed this new concept in cancer biology: tumor reprogramming (also known as cancer cell plasticity), and further investigated this process with collaborators and today it is one of the main research interests in my lab.

a. T Marumoto, A Tashiro, **D Friedmann-Morvinski**, M Scadeng, Y Soda, F H. Gage and I M. Verma. “Development of a novel mouse glioma model using lentiviral vectors”. Nature Medicine 2009 January; 15(1):110-6.
b. Soda Y, Marumoto T, **Friedmann-Morvinski D**, Soda M, Liu F, Michiue H, Pastorino S, Yang M, Hoffman RM, Kesari S and Verma IM. “Transdifferentiation of Glioblastoma Cells into Vascular Endothelial Cells”. Proc Natl Acad Sci U S A. 2011 March 15:108(11): 4274-80.
c. **Friedmann-Morvinski D**, Bushong EA, Ke E, Soda Y, Marumoto T, Singer O, Ellisman MH and Verma IM. “Dedifferentiation of Astrocytes and Neurons by Oncogenes can Induce Gliomas in Mice”. SCIENCE 2012 Nov 23;338(6110):1080-4
d. **Dinorah Friedmann-Morvinski*,** Vipul Bhargava*, Shakti Gupta, Inder M. Verma and Shankar Subramaniam. “Identification of therapeutic targets for glioblastoma by network analysis” Oncogene 2016 Feb 5;35(5):608-20

4. In my independent lab, we focus on the mechanisms of cancer cell plasticity and the contributions of the tumor microenvironment to this process. We use an integrative approach to study brain tumor (glioma)-specific neurobiology and oncobiology, and state-of-the-art mouse models of the disease to unveil the cross-

talk between tumor cells and non-neoplastic cells in the tumor microenvironment. We identified TNC, and ECM component, to play an important role in orchestrating glioma plasticity. Exploring the longitudinal landscape of GBM induced by different oncogenic drivers, we uncover bone-marrow derived neutrophils to infiltrate mesenchymal GBM tumors from early stages and through progression. We were able to show systemic reprogramming of bone-marrow derived neutrophils, a switch from anti- to pro-tumorigenic, which indicates an effect of the tumor in the polarization of these cells during the disease progression.
Using our immunocompetent GBM models we were able to identify p32 to be expressed on the surface of glioma cells, making it a suitable tumor associated antigen for redirected CAR T cell therapy. We generate p32 CAR T cells and find them to recognize and specifically eliminate p32 expressing glioma cells and tumor derived endothelial cells.

a. Angel I, Pilo Kerman O, Rousso-Noori L, **Friedmann-Morvinski D**. Tenascin C promotes cancer cell plasticity in mesenchymal glioblastoma. Oncogene. 2020 Nov;39(46):6990-7004.
b. Magod P, Mastandrea I, Rousso-Noori L, Agemy L, Shapira G, Shomron N, **Friedmann-Morvinski D**. Exploring the longitudinal glioma microenvironment landscape uncovers reprogrammed pro-tumorigenic neutrophils in the bone marrow.
c. Rousso-Noori L, Mastandrea I, Talmor S, Waks T, Globerson Levin A, Haugas M, Teesalu T, Alvarez-Vallina L, Eshhar Z, **Friedmann-Morvinski D**. P32-specific CAR T cells with dual antitumor and antiangiogenic therapeutic potential in gliomas. Nat Commun. 2021 Jun 14;12(1):3615.

D. <u>List of publications (past 5 years)</u>

1. Ilouz R, Lev-Ram V, Bushong EA, Stiles TL, **Friedmann-Morvinski D**, Douglas C, Goldberg G, Ellisman MH, Taylor SS. “Isoform-specific subcellular localization and function of protein kinase A identified by mosaic imaging in mouse brain”. Elife 2017 Jan 12; doi: 10.7554/eLife.17681.

2. Mazor R*, **Friedmann-Morvinski D***, Alsaigh T, Kleifeld O, Kistler EB, Rousso-Noori L, Huang C, Li JB, Verma IM, Schmid-Schönbein GW. “Cleavage of the leptin receptor by matrix metalloproteinase-2 promotes leptin resistance and obesity in mice. Sci Transl Med, 2018 Aug 22:10(455) doi: 10.1126/scitranslmed.aah6324. **co-first authors and corresponding authors.*

3. Kand D, Pizarro L, Angel I, Avni A, **Friedmann-Morvinski D**, Weinstain R. Organelle-Targeted BODIPY Photocages: Visible-Light-Mediated Subcellular Photorelease. Angew Chem Int Ed Engl. 2019 Mar 26;58(14):4659-4663.

4. Margalit S, Avraham S, Shahal T, Michaeli Y, Gilat N, Magod P, Caspi M, Loewenstein S, Lahat G, **Friedmann-Morvinski D**, Kariv R, Rosin-Arbesfeld R, Zirkin S, Ebenstein Y.5-Hydroxymethylcytosine as a clinical biomarker: Fluorescence-based assay for high-throughput epigenetic quantification in human tissues. Int J Cancer. 2019 Jun 18. doi: 10.1002/ijc.32519.

5. Säälik P, Lingasamy P, Toome K, Mastandrea I, Rousso-Noori L, Tobi A, Simón-Gracia L, Hunt H, Paiste P, Kotamraju VR, Bergers G, Asser T, Rätsep T, Ruoslahti E, Bjerkvig R, **Friedmann-Morvinski D***, Teesalu T*. Peptide-guided nanoparticles for glioblastoma targeting. J Control Release. 2019 Aug 28;308:109-118. doi: 10.1016 /j.jconrel.2019.06.018. *Co-corresponding authors.

6. Kand D, Liu P, Navarro MX, Fischer LJ, Rousso-Noori L, **Friedmann-Morvinski D**, Winter AH, Miller EW, Weinstain R.Water-Soluble BODIPY Photocages with Tunable Cellular Localization. J Am Chem Soc. 2020 Mar 18;142(11):4970-4974.

7. Angel I, Pilo Kerman O, Rousso-Noori L, **Friedmann-Morvinski D**. Tenascin C promotes cancer cell plasticity in mesenchymal glioblastoma. Oncogene. 2020 Nov;39(46):6990-7004

8. CRISPR/Cas9 Genome Editing using Targeted Lipid Nanoparticles for Cancer Therapy. Rosenblum D, Gutkin A, Kedmi R, RAmishetti, S, Veiga N., Jacoby AM, Schubert MS, **Friedmann-Morvinski D**, Cohen ZR, Behlke MA, Lieberman J and Peer D. Sci Adv. 2020 Nov 18;6(47):eabc9450.

9. P-selectin axis plays a key role in microglia immunophenotype and glioblastoma progression. Yeini E, Ofek P, Pozzi S, Albeck N, Ben-Shushan D, Tiram G, Golan S, Kleiner R, Sheinin R, Israeli Dangoor S, Reich-Zeliger S, Grossman R, Ram Z, Brem H, Hyde TM, Magod P, **Friedmann-Morvinski D**, Madi A, Satchi-Fainaro R. Nat Commun. 2021 Mar 26;12(1):1912.

10. P32-specific CAR T cells with dual antitumor and antiangiogenic therapeutic potential in gliomas. Rousso-Noori L, Mastandrea I, Talmor S, Waks T, Globerson Levin A, Haugas M, Teesalu T, Alvarez-Vallina L, Eshhar Z, **Friedmann-Morvinski D**. Nat Commun. 2021 Jun 14;12(1):3615.

11. Exploring the longitudinal glioma microenvironment landscape uncovers reprogrammed pro-tumorigenic neutrophils in the bone marrow. Magod P, Mastandrea I, Rousso-Noori L, Agemy L, Shapira G, Shomron N, **Friedmann-Morvinski D**. Cell Rep. 2021 Aug 3;36(5):109480

12. Isolation and characterization of the immune cell fraction from murine brain tumor microenvironment. Mastandrea I, Sher D, Magod P, **Friedmann-Morvinski D**. STAR Protoc. 2022 Jan 20;3(1):101106.

13. Differentiated glioma cell-derived fibromodulin activates integrin-dependent Notch signaling in endothelial cells to promote tumor angiogenesis and growth. Sengupta S, Mondal M, Prasasvi KR, Mukherjee A, Magod P, Urbach S, **Friedmann-Morvinski D***, Marin P*, Somasundaram K*. Elife. 2022 Jun 1;11:e78972. *co-corresponding authors.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=friedmann-morvinski+d

E. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Individual Research Grant– Israel Science Foundation (ISF) 10/2020-09/2025
Unveiling the role of the extracellular matrix and its key players and modulators in glioma cell plasticity
Role: PI

Israel Precision Medicine Program (IPMP) 10/2020-09/2024
Immunotherapy of glioblastoma with metabolically superior bi-specific CAR T-cells
Role: co-PI

EuroNanoMed3 04/2022-03/2025
LDL-like nanoparticles for CAR-T-based glioblastoma immunotherapy
Role: co-PI

Israel Cancer Research Fund (ICRF)- Initiative in Pediatric cancer (09/2022-08/2025)
Generation, characterization and treatment of novel murine pedLGG models
Role: PI

Israel Cancer Association (ICA) (01/2023-12/2023)
Characterization of Glioma Tumor Microenvironment Following HOXD8 Knockdown and Identification of Factors that Modulate Tumor Aggressiveness
Role: co-PI

Pending Research Support

Israel Cancer Research Fund (ICRF)- Research Grant
Unveiling the role of HOXD8 in glioblastoma and brain metastases
Role: co-I

Israel Cancer Research Fund (ICRF)- Research Grant
Elucidating the role of PROS1 in GBM plasticity
Role: co-I