BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Neta Erez	**Full Professor**, Tel Aviv University. **Vice Dean, Faculty of Medicine**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Faculty of Agriculture, The Hebrew University, Israel.	B.Sc.	1992-1995	Animal Sciences
Department of Molecular Cell Biology and Department of Immunology, Weizmann Institute of Science, Israel. PI: Prof. Varda Rotter and Prof. Irun Cohen.	M.Sc.	1995-1997	Immunology, Molecular Cell Biology
Department of Molecular Cell Biology and Department of Immunology, Weizmann Institute of Science, Israel. PI: Prof. Varda Rotter and Prof. Irun Cohen.	Ph.D.	1998-2004	Molecular Cell Biology, Cancer Research
Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel. PI: Prof. Varda Rotter.	Postdoctoral Fellow	2004-2005	Molecular Cell Biology, Cancer Research
University of California, San Francisco, San Francisco, CA. PI: Prof. Douglas Hanahan	Postdoctoral Fellow	2005-2010	Tumor Biology

A. Personal Statement

It is my conviction that understanding tumor metastasis is the most important challenge of cancer research today and therefore it is the main focus of my lab. I believe that tumors should be studied with a comprehensive approach, as multi-cellular organs that maintain complex interactions with multiple types of host cells. Throughout my training and career as a scientist, my research has been focused on tumor biology and mechanisms of carcinogenesis. I have extensive experience in working with mouse models of cancer to characterize interactions between tumors and their microenvironment, and studying tumor metastasis is the major interest of my lab. Recent studies from my lab focused on the role of the microenvironment in breast cancer progression and metastasis (*Journal of Experimental Medicine* 2018, *Nature Communications* 2019, *Cancer Research* 2020, *eLife* 2021, *Nature Communications* 2022), and on neuroinflammation in melanoma brain metastasis (*Cancer Research* 2016, *International Journal of Cancer* 2019, *Cell Reports* 2019, *Nature Cancer*, *accepted*). My expertise in tumor biology, as well as my past accomplishments, make me most suitable to successfully accomplish our goals. I am highly motivated and confident in our ability to perform cutting edge research and to make a significant contribution to the development of novel strategies to combat mortality from cancer metastasis.

B. Positions and Honors (in chronological order).

Positions

2010-2015	**Assistant Professor (Senior Lecturer),** Department of Pathology, Faculty of Medicine, Tel Aviv University, Israel.
2016-2018	**Tenured Assistant Professor (Senior Lecturer),** Department of Pathology, Faculty of Medicine, Tel Aviv University, Israel.
2017-2022	**Department Chair**, Department of Pathology, Faculty of Medicine, Tel Aviv University, Israel.
2018-2022	**Associate Professor**, Department of Pathology, Faculty of Medicine, Tel Aviv University, Israel.
2022- present	**Full Professor.** Department of Pathology, Faculty of Medicine, Tel Aviv University, Israel.
2022- present	**Vice Dean for Preclinical Teaching Excellence & Mentoring,** Faculty of Medicine, Tel Aviv University, Israel.

Honors and Awards (selected)

2020	**Nature Research Award for Mentoring in Science.**
2019	Dean's Award for Excellence in Teaching. Faculty of Medicine, Tel Aviv University.
2018	City of Nes-Zionna Award for Contribution to Science and Medicine.
2017	**Tel Aviv University Rector Award for Excellence in Teaching**.
2017	Selected for Young Scientists Forum of the Israel Academy of Sciences.
2016	Dean's Award for Excellence in Teaching. Faculty of Medicine, Tel Aviv University.
2015	**European Research Council (ERC) Starting Grant.**
2013	Best Short Talk Prize - Beatson International Cancer Conference.
2013	Tel Aviv University Award for Commitment to the Advancement of Women in Science.
2011	Israel Cancer Association **Outstanding Grant Award**.
2005	**Cancer Research Institute (CRI) Postdoctoral Fellowship**.
2002	Katzir-Katchalsky Travel Fellowship (Weizmann Institute of Science).
2000	NIH Fellowship Award for the 10th International p53 Workshop.
1999	UICC International Cancer Technology Transfer (ICRETT) Fellowship.
1997	Feinberg Graduate School Prize for Outstanding Master Thesis, Weizmann Institute of Science, Israel.
1995	*Magna cum laude* in Animal Sciences, Faculty of Agriculture, Hebrew University, Israel.
1992-1995	Dean's List, Faculty of Agriculture, Hebrew University, Israel.

Selected Membership of Boards and Scientific Advisory activities (last 5 years):

2022-present	Elected Board Member, European Association for Cancer Research (**EACR**).
2022-present	**AACR** Tumor Microenvironment Working Group (TME) Steering Committee.
2022	Scientific Advisory Committee, The Rothschild Fellowships for Physician-Researchers.
2021	AACR Annual Meeting 2022, Scientific Program Subcommittee.
2020-2025	**Scientific Advisory Committee**, Worldwide Cancer Research.
2020-present	Elected Board Member, Metastasis Research Society (**MRS**).
2020-present	Elected **Vice President** (and President Elect), Israeli Society for Cancer Research (**ISCR**).
2018-present	Board Member, Israeli Society for Cancer Research (ISCR).

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 for Cancer Research (ISCR).
2021-present:	**Chair, PhD Oversight Committee**, Faculty of Medicine, Tel Aviv University.
2020-2021	**Chair**, MSc Student Oversight Committee, Faculty of Medicine, Tel Aviv University.
2021	Organizer, EACR Conference: The Structural Microenvironment, March 2022.
2021	Organizer, Annual Meeting of the Israeli Society for Cancer Research (ISCR).
2021	Session Chair and Organizer, AACR Annual Meeting 2021,
2020-present	**Co-organizer, "Nurturing Women Scientists" Mentoring Program**, Faculty of Medicine, Tel Aviv University.
2019	Organizer, Stress and Inflammation in Tumor Progression and Metastasis, Weizmann Institute, Israel.
2018-2022	Member, Faculty Search and Hiring Committee, Faculty of Medicine, Tel Aviv University.

Professional Memberships

2010-present	**Member,** Israeli Society for Cancer Research (**ISCR**).
2010-present	**Member,** European Association for Cancer Research (**EACR**).
2012-present	**Active Member**, American Association for Cancer Research (**AACR**).
2015-present	**Member**, Metastasis Research Society (**MRS**).

C. Contribution to Science

1. My early career research focused on tumor immunology and was a collaborative work between the labs of Prof. Irun Cohen and Prof. Varda Rotter at the Weizmann Institute of Science. I showed that immunity to p53, induced by idiotypic vaccines against different p53 domains can protect mice against tumor development and reduce the number of established metastases (Erez-Alon et al., *Cancer Research* 1998). Interestingly, we found that autoantibodies to the C-terminal domain of p53 are also associated with the autoimmune disease Systemic Lupus Erythematosus (Herkel* and Erez-Alon* et al., *European Journal of Immunology* 2000). This work was the basis for several follow-up papers in which I am a co-authour, using tools that I established (Herkel, Mimran, Erez et al., *Journal of Autoimmunity* 2001, Herkel, Kam, Erez et al., *European Journal of Immunology.* 2004). Furthermore, my work in mice was the basis for an independent clinical trial utilizing idiotypic immunity to p53 as a tumor vaccine, and to several patents. Some of the tools developed in this work were recently used for studies of autoimmunity and inflammation (Herkel, Schrader, Erez et al. *Immunology* 2017).

2. My Ph.D. research was performed in the lab of Prof. Varda Rotter at the Weizmann Institute of Science. I initiated a collaboration with Prof. Andrei Gudkov (then at UIC in Chicago) and spent a semester in his lab. As a result of this collaboration, I constructed a Genetic Suppressor Elements (GSE) library. GSEs are short fragments of genes that inhibit the function of the gene from which they are derived. In a functional genetic screen, I have identified GSEs that conferred primary mouse cells with resistance to drug-induced growth arrest and cloned a novel gene: Falkor/PHD1 (Erez et al., *Oncogene* 2002). This gene was cloned in parallel by others and shown to be a Prolyl Hydroxylase (PHD1), modulating the level of the transcription factor HIF-1a in an oxygen dependent manner. I further characterized this gene, and showed that expression of PHD1 suppressed accumulation of HIF-1a and secretion of VEGF following hypoxia, and inhibited tumor growth *in vivo*, in correlation with increased necrosis and a striking decrease in microvessel density (Erez et al., *Cancer Research* 2003). To characterize the regulation of PHD1 expression, I cloned the human PHD1 gene promoter, and showed that its expression is reduced under hypoxic conditions, thus creating a functional link between oxygen availability and hypoxia-induced gene expression (Erez et al.,

FEBS Letters 2004). My Ph.D. research, and its implications for tumor growth, angiogenesis, and the pathology of oxygen sensing had been cited in many papers and reviews.

3. My postdoctoral research in the laboratory of Prof. Doug Hanahan was focused on tumor biology and tumor-stroma interactions. **I discovered a novel role for cancer-associated fibroblasts (CAFs) in mediating tumor-promoting inflammation.** I isolated fibroblasts from fresh mouse and human tissues and performed expression profiling of *in vivo*-derived CAFs. My findings indicated that CAFs express a pro-inflammatory gene signature, starting already at pre-neoplastic lesions, and showed that fibroblasts are reprogrammed to become pro-inflammatory CAFs that recruit macrophages to the tumor microenvironment. Functional inhibition of pro-inflammatory signaling in CAFs inhibited tumor growth, suggesting for the first time that fibroblast-mediated inflammation plays a crucial role in generating a tumor-promoting microenvironment (Erez et al. *Cancer Cell* 2010). ***These findings created a paradigm shift, reciprocated by many other studies and established CAFs as central players in tumor-promoting inflammation.*** My article in Cancer Cell was accompanied by a preview by Alberto Mantovani (*Cancer Cell* 2010). The study was cited >1400 times, designated in Web of Science a "Highly Cited Paper": Top 1% of the academic field of Molecular Biology & Genetics, and *Recommended in Faculty of 1000:* https://f1000.com/prime/2137001#recommendations-content.

4. In October 2010 I established my lab at Tel Aviv University, and initiated a highly competitive research program that focuses on cutting-edge research in the field of **tumor biology, with special emphasis on cancer-promoting inflammation and the metastatic microenvironment.** With 15 excellent PhD and MD-PhD students, MSc students and postdoctoral fellows, we uncover the complex interactions between cancer cells, stromal cells and immune cells that contribute to tumor progression and metastasis. We combined transgenic mouse models of cancer and clinical data to uncover the role of inflammation and cancer-associated fibroblasts (CAFs) in facilitating breast cancer and lung metastasis. We demonstrated that pro-inflammatory signalling by CAFs is operative in human breast and ovarian carcinomas, and is correlated with progression (Erez et al, *BBRC* 2013). The method we developed for isolation of fibroblasts from fresh normal and tumor tissues is used by many other labs (Sharon et al. *JoVE* 2013). In an effort to investigate how normal mammary fibroblasts are activated to CAFs, we performed proteomics analysis of breast cancer secretome, and found that tumor-derived Osteopontin reprograms resident fibroblasts to become pro-inflammatory and tumor promoting in breast cancer (Sharon et al. *Cancer Research* 2015). In addition, we demonstrated that fibroblasts drive an immunosuppressive and growth-promoting microenvironment in breast cancer, mediated by Chi3L1 secretion (Cohen et al. *Oncogene* 2017). The finding that CAFs mediate immune suppression elucidated an important new role for CAFs in modulating the immune microenvironment which we summarized in an invited review (*Frontiers in Immunology* 2019). Another breakthrough came when we addressed a long-standing question in the field regarding the origin of CAFs: we identified a novel subpopulation that is specifically recruited from the bone marrow to breast tumors and lung metastasis, and characterized their distinct functional role. By performing adoptive bone-marrow transplantations in a mouse model of breast cancer, we demonstrated that the expression of PDGFRα distinguishes two functional CAF populations in breast tumors and in lung metastases. This study was published (Raz, Cohen et al., *Journal of Experimental Medicine* 2018), and highlighted in a preview by David Tuveson in the same issue.

5. Another major focus of research in the lab is studying the role of **neuroinflammation in melanoma brain metastasis.** Using patient-derived xenografts isolated from brain metastases, we showed that astrocyte-derived IL-23 facilitates melanoma cell invasiveness into brain (Klein et al. *Journal of Pathology* 2015). In addition, we demonstrated that the chemokine receptor CCR4 is highly expressed by brain metastasizing melanoma cells and is functionally important for formation of brain micrometastases (Klein et al. *Oncotarget* 2017). In order to study the early stages of brain metastases formation, we established a novel mouse model of spontaneous melanoma brain metastasis in immunocompetent mice, and developed molecular tools for quantitative detection of brain micrometastases. We demonstrated that brain micrometastases are associated with instigation of astrogliosis, neuroinflammation, and hyperpermeability of the blood-brain barrier. Furthermore, we showed a functional role for astrocytes in facilitating the initial growth of melanoma cells (Schwartz et al. *Cancer Research* 2016). We also found that inflammatory reprograming of the metastatic stroma by melanoma cells is mediated partially by exosomes that signal to

astrocytes and lung fibroblasts (Gener Lahav et al. *International Journal of Cancer,* 2019). Moreover, we characterized the role of astrocytes in mediating neuroinflammation that supports brain metastasis. We showed that activated astrocytes upregulated CXCL10, and demonstrated that the CXCL10-CXCR3 signaling axis is hijacked to support melanoma brain tropism (Doron, Amer et al. *Cell Reports* 2019). We further characterized the instigation of neuroinflammation in breast cancer and melanoma brain metastasis and identified LCN2 as a central player in the crosstalk between innate immune cells and astrocytes (Adler, Zait et al., *Nature Cancer*, accepted).

6. My current research focus in the lab is based on the conviction that uncovering the mechanisms that facilitate tumor metastasis is an urgent and unmet clinical need. Our research programs combine state-of-the-art transgenic mouse models with basic and pre-clinical approaches to reveal the molecular events at the earliest stages of metastasis. We uncovered a novel mechanism by which CAFs promote tumor progression: we found that CAFs can function as sensors of tissue damage in breast tumors, resulting in activation of the NLRP3 inflammasome, which facilitated tumor growth and lung metastasis. Thus, we showed that activation of the NLRP3 inflammasome in cancer-associated fibroblasts links tissue damage with tumor-promoting inflammation (Ershaid, et al., *Nature Communication* 2019). To characterize for the first time the co-evolution of metastases-associated fibroblasts, we isolated lung fibroblasts in an unbiased manner from normal mice, or from mice with micro- or macro-metastases and profiled their transcriptome. We demonstrated that fibroblasts in lung metastases are transcriptionally dynamic and plastic, and revealed stage-specific gene signatures that imply functional tasks, including extracellular matrix remodeling, stress response and shaping the inflammatory microenvironment. Furthermore, we identified *Myc* as a central regulator of fibroblast rewiring and found that stromal upregulation of *Myc* transcriptional networks is associated with worse survival in human breast cancer. (Shani et al. *eLife 2021*). Moreover, we showed that CAFs in lung metastases upregulate IL-33 and facilitate breast cancer metastasis by modifying the immune microenvironment, by driving type-2 immunity (Shani et al. *Cancer Research 2020*) and by mediating resistance to chemotherapy (Monteran, Ershaid et al. *Nature Communication* 2022). To further deepen our insight on mechanisms of metastasis, and since bones are the most prominent site of breast cancer metastasis, we established a mouse model of spontaneous bone metastasis and characterized the bone metastatic microenvironment (Monteran et al. *Scientific Reports*, 2020).

- As a result of my expertise in the field of the tumor microenvironment and metastasis, I was invited to write review articles and News & Views in multiple high impact journals including *Nature*, *Nature Cell Biology*, *Journal of Pathology*, *Cancer Research*, *Trends in Cell Biology*, *Trends in Cancer* and *Nature Cancer*.

Complete List of published work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/neta.erez.1/bibliography/public/

D. Mentorship and Other Intellectual Contributions

In addition to my research achievements I am also an enthusiastic mentor and advocate for women in science. I consider mentoring one of my most important missions. I dedicate time and effort to nurturing young scientists (in addition to my own students) by teaching a highly successful “scientific soft skills” course at the Tel Aviv University, by being a professional mentor to young PIs, and by co-organizing a program for mentoring women PhD students at the Tel Aviv University Faculty of Medicine. Acknowledging my contributions, I was awarded in 2020 The **Nature Research Award for Mentoring in Science**. In addition, I am Chair of the Faculty of Medicine PhD Committee and I was recently nominated Vice Dean for Excellence in Teaching and Mentoring at the Faculty of Medicine. In both capacities I dedicate time and effort to improve teaching programs and include personal and career development platforms in the nurturing of young researchers.