BIOGRAPHICAL SKETCH

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NAME: **Ronai, Ze'ev**

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

POSITION TITLE: Professor and Chief Scientific Advisor, Tumor Initiation and Maintenance Program

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
The Hebrew University, Jerusalem, Israel	B.S.	1980	Biology
The Hebrew University, Jerusalem, Israel	M.S.	1982	Microbiology
The Hebrew University, Jerusalem, Israel	Ph.D.	1985	Immunobiology
Columbia University, New York, New York	Postdoc	1988	Molecular Biology

A. Personal Statement

My passion for science is reflected in my dedication to solve critical unmet clinical problems in cancer, with focus of my research on epigenetic mechanisms that underlie tumor development, progression and resistance. Our studies often provided new fundamental understanding for transcription factor and ubiquitin ligase regulation and function in cancer, resulting in novel paradigms. Research conducted in my lab is performed in cell-based setting (cell biology) complemented by biochemistry and mouse models, and is subject to validation in human tumor specimens and is validated using extensive bioinformatics tools. Our studies are carried out in collaboration with clinicians (oncologists and pathologists) and experts (bioinformaticians), allowing an assessment in human samples and establish their significance for clinical care and future development of novel therapeutic modalities. Among my major scientific contributions were the development of sensitive PCR enabling detection of mutant Ras oncogene in normal appearing tissues, defining the early days of personal medicine; the appreciation of rewired signal transduction in cancer and the fundamental understanding of ubiquitin ligases role in key cellular processes (i.e. hypoxia, UPR), which define cancer development, progression, and therapy resistance.

The following highlights fundamental discoveries which established novel paradigms.

- Nakayama, K., Frew, I.J., Hagensen, M., Skals, M., Habelhah, H., Bhoumik, A., Kadoya, T., Erdjument-Bromage, H., Tempst, P., Frappell, P.B., Bowtell, D.D., Ronai, Z. (2004) Siah2 regulates stability of prolylhydroxylases, controls HIF1alpha abundance, and modulates physiological responses to hypoxia, Cell 117:941-52. *Paradigm shift in understanding ubiquitin ligase control of oxygen sensors and their implications for hypoxia.*
- Lopez-Bergami, P., Huang, C., Goydos, J.S., Yip, D., Bar-Eli, M., Herlyn, M., Smalley, K.S., Mahale, A., Eroshkin, A., Aaronson, S., Ronai, Z. (2007) Rewired ERK-JNK signaling pathways in melanoma, Cancer Cell 11:447-60. PMCID: PMC1978100. *Demonstrated the significance of rewired signaling for melanoma, through linking ERK with JNK signaling.*
- Lau, E., Kluger, H., Varsano, T., Lee, K.Y., Scheffler, I., Rimm, D.L., Ideker, T., Ronai, Z.A. (2012) PKCε regulates ATF2 availability to alter mitochondrial permeability following genotoxic stress. Cell 148:543-55. PMCID: PMC3615433. *Paradigm shift in understanding transcription factor ability to function as oncogene or tumor suppressor gene.*
- Li Y, Tinoco R, Elmén L, Segota I, Xian Y, Fujita Y, Sahu A, Zarecki R, Marie K, Feng Y, Khateb A, Frederick DT, Ashkenazi SK, Kim H, Perez EG, Day CP, Segura Muñoz RS, Schmaltz R, Yooseph S, Tam MA, Zhang T, Avitan-Hersh E, Tzur L, Roizman S, Boyango I, Bar-Sela G, Orian A, Kaufman RJ,

Bosenberg M, Goding CR, Baaten B, Levesque MP, Dummer R, Brown K, Merlino G, Ruppin E, Flaherty K, Ramer-Tait A, Long T, Peterson SN, Bradley LM, Ronai ZA. Gut microbiota dependent anti-tumor immunity restricts melanoma growth in Rnf5$^{-/-}$ mice. ***Nat Commun.*** 2019; 10(1):1492. PMCID: PMC6445090. *First demonstration for the importance of ubiquitin ligase in control of UPR which in turn define microbiota organization impacting anti-tumor immunity.*

B. Positions and Honors

Research and/or Professional Appointments:

1982 – 1985	Ph.D., Lautenberg Center, Hebrew University, Jerusalem, Israel.
1985 – 1989	Postdoctoral Fellow, Columbia University, NY, Mentor I.B. Weinstein.
1988 – 1998	Head, Molecular Carcinogenesis Program, American Health Foundation.
1989 – 1997	Assistant/Associate Prof. Depts Microbiology Pathology, NY Med College, Valhalla, NY.
1993 – 1998	Consultant, Department of Medicine, Memorial Sloan Kettering, New York, NY.
1997 – 1999	Associate Professor, Ruttenberg Cancer Center, Mount Sinai School of Medicine, NY.
1999 – 2005	Professor, Ruttenberg Cancer Center, MSSM, New York, NY.
2004 – 2013	Director, and Professor, Signal Transduction Prog, Sanford-Burnham Medical Research Institute (SBMRI), La Jolla, CA.
2005 – 2016	Adjunct Professor, Molecular Pathology Program, UC San Diego, La Jolla, CA.
2008 – 2014	Associate/Deputy Director, NCI Cancer Center, SBMRI, La Jolla, CA.
2013 – Present	Professor, Tumor Initiation and Maintenance Program, SBMRI, La Jolla, CA.
2013 – 2016	Scientific Director, Sanford-Burnham Medical Research Institute, La Jolla, CA.
2016 – 2018	Professor & Co-Director, Technion Integrated Cancer Center, Technion, Haifa, Israel.
2016 – Present	Chief Scientific Advisor, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA.
2020 – Present	Acting Director, NCI Cancer Center SBP Discovery, La Jolla, CA.

Professional Activities:

NIH grant review: 1991 NIH committee for RFA Design in Radiation Biology; 1994–1999 Member Cancer Study Section Tobacco Research Program, UCSF; 1995–1997 NCI Multidisciplinary Special Emphasis Study Section; 1995 NIH Review Committee for Program Project on Radiation Biology; 1996–2001 Member of NCI Chemical Pathology Study Section; 2001 NIH Review for PPG on Melanoma Biology; 2007–2009 NIH TPM Study Section; 2012 NCI Provocative Questions. 2012–present Ad Hoc NCI study sections CAMP, TCB, OIA/R35 and others.

Scientific Advisory Boards: P01, University of Arizona, Tucson; P01, Wistar Institute, Philadelphia; SPORE, University of Colorado, Denver, MGH, Boston. ***Conference Organization*****:** 1994 Chair, Symposium on Int. Cell Diff. Conf Hiroshima, Japan; 1996 Organizing Committee, Symposium on Cancer & Biotechnology, Nice, France; Organizing committee, 4th International Symposium Cancer Biotech., Geneva, Switzerland; 2000 Co-Chair, NIH workshop on Melanoma; 2004, 2006, 2010 Co-organizer, Ubiquitin Workshop, Hebrew University, Jerusalem; 2007 Co-organizer International Melanoma Conference. 2015, June, Ubiquitin Workshop, Southern China; June 2015 Melanoma workshop Iceland. ***Editorial***: 1996–98 and 2001–2003 *Carcinogenesis*; 1997–2001 *Cancer Prevention and Detection*; 1999–2002 Associate Editor *Clinical Cancer Research*; 2001–present *Molecular Carcinogenesis*; 2002–present *Cancer Biology and Therapy*; 2002–2007 *Journal of Biological Chemistry*; 2002–present *Molecular and Cellular Biology*; 2007–2010 Associate Editor *Cancer Research*; 2007–2009 Executive Editor *Pigment Cell and Melanoma Research;* 2010–2012 Editor-in-Chief *Pigment Cell and Melanoma Research. Frequent reviewer Cell, Mol. Cell, Cancer Cell, Science, Science Sig. Nature, Nat. Cell Biol, Nat. Med. Nat Comm PNAS, EMBO J, PLoS journals, and others.*

Awards and Honors:

1982	Prize from the Hebrew University for MS. Outstanding Thesis.
1984	Awarded the Golda Meir Fellowship.
1992	JPCR Fellowship from National Cancer Center, Tokyo.
1995	Princess Takamatsu Symposium, Tokyo; Hiroshima Cancer Symposium.
2000	Dean lecture series – Mount Sinai School of Medicine.
2001	Karolinska Nobel Conference on Ubiquitin, Stockholm, Sweden.
2002, 2005	Banbury Conference CSH, Melanoma biology.
2004	Karolinska Nobel Conference on Hypoxia, Stockholm, Sweden.
2008	Keynote speaker, Melanoma Symposium, Penn State University.

2012 NCI Director Lecture Series.
2013 UCSD Cancer Center Director's Seminar Series, speaker.
2014 UCI Cancer Center Retreat, Keynote speaker.
2016 Frontiers in Cancer Research at the Nobel Forum, Karolinska Institute, Stockholm, Sweden.
2016 Society Melanoma Research, Lifetime Achievement Award, Boston, MA.
2019 Keynote speaker, C3 (UCSD; Salk; SBP) cancer centers symposia.
2020 Distinguished Scientist Seminar, University of Maryland, MD.
2020 Keynote speaker, Cancer Biology & Signaling Program Retreat, La Jolla, CA.

C. Contributions to Science (over 22,000 citations; H-index >81; i10 index >210; >300 publications)

Significant discoveries from my lab include:

***Rewired signaling in cancer**. Cross talk between diverse signal transduction and metabolic pathways in cancer.*

- Ivanov VN, Bhoumik A, Krasilnikov M, Raz R, Owen-Schaub LB, Levy D, Horvath CM, Ronai Z. Cooperation between STAT3 and c-jun suppresses Fas transcription. ***Mol Cell**.* 2001; 7(3):517-28. PMID: 11463377.
- Lau E, Feng Y, Claps G, Fukuda MN, Perlina A, Donn D, Jilaveanu L, Kluger H, Freeze HH, Ronai ZA. The transcription factor ATF2 promotes melanoma metastasis by suppressing protein fucosylation. ***Sci Signal**.* 2015; 8(406):ra124. PMCID: PMC4818095.
- Claps G, Cheli Y, Zhang T, Scortegagna M, Lau E, Kim H, Qi J, Li JL, James B, Dzung A, Levesque MP, Dummer R, Hayward NK, Bosenberg M, Brown KM, Ronai ZA. A transcriptionally inactive ATF2 variant drives melanomagenesis. ***Cell Rep**.* 2016; 15(9):1884-92. PMCID: PMC4889472.
- Pathria G, Scott DA, Feng Y, Sang Lee J, Fujita Y, Zhang G, Sahu AD, Ruppin E, Herlyn M, Osterman AL, Ronai ZA. Targeting the Warburg effect via LDHA inhibition engages ATF4 signaling for cancer cell survival. ***EMBO J**.* 2018; 37(20). pii: e99735. PMCID: PMC6187221.
- Pathria, G., Lee, JS., Hasnis, E., Tandoc, K., Scott, DA., Verma, S., Feng, Y., Larue, Lionel., Sahu, AD., Topisirovic, I., Ruppin, Ronai, ZA. Translational Reprogramming Marks Adaptation to Asparagine Restriction in Cancer. ***Nat. Cell Biol.*** 2019; 21(12):1590-1603. PMCID: PMC7307327.

***Novel players in control of cellular stress and homeostasis**. Stress kinases induced by DNA breaks, p53 and c-Jun control by ubiquitin, redox and ubiquitination controls stress kinases, regulation of hnRNPK and eIF4F*

- Fuchs SY, Dolan L, Davis RJ, Ronai Z. Phosphorylation-dependent targeting of c-Jun ubiquitination by Jun N-kinase. ***Oncogene***. 1996; 13(7):1531-5. PMID: 8875991.
- Adler V, Yin Z, Fuchs SY, Benezra M, Rosario L, Tew KD, Pincus MR, Sardana M, Henderson CJ, Wolf CR, Davis RJ, Ronai Z. Regulation of JNK signaling by GSTp. ***EMBO J***. 1999; 18(5):1321-34. PMCID: PMC1171222.
- Fuchs SY, Adler V, Buschmann T, Yin Z, Wu X, Jones SN, Ronai Z. JNK targets p53 ubiquitination and degradation in nonstressed cells. ***Genes Dev***. 1998; 12(17):2658-63. PMCID: PMC317120.
- Habelhah H, Shah K, Huang L, Ostareck-Lederer A, Burlingame AL, Shokat KM, Hentze MW, Ronai Z. ERK phosphorylation drives cytoplasmic accumulation of hnRNP-K and inhibition of mRNA translation. ***Nat Cell Biol**.* 2001; 3(3):325-30. PMID: 11231586.
- Feng Y, Pinkerton AB, Hulea L, Zhang T, Davies MA, Grotegut S, Cheli Y, Yin H, Lau E, Kim H, De SK, Barile E, Pellecchia M, Bosenberg M, Li JL, James B, Hassig CA, Brown KM, Topisirovic I, Ronai ZA. SBI-0640756 attenuates the growth of clinically unresponsive melanomas by disrupting the eIF4F translation initiation complex. ***Cancer Res***. 2015; 75(24):5211-8. PMCID: PMC4681635.

***Ubiquitin Ligases / post-translational modification controls fundamental regulatory processes**. β-TRCP control of IκB and β-catenin stability, Siah2 in mitochondrial dynamics, Siah2 fine tunes the UPR, ATF2 oncogenic function via glycosylation and dominant negative splice variant.*

- Fuchs SY, Chen A, Xiong Y, Pan ZQ, Ronai Z. HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IkappaB and beta-catenin. ***Oncogene***. 1999; 18(12):2039-46. PMID: 10321728.

- Kim H, Scimia MC, Wilkinson D, Trelles RD, Wood MR, Bowtell D, Dillin A, Mercola M, Ronai ZA. Fine-tuning of Drp1/Fis1 availability by AKAP121/Siah2 regulates mitochondrial adaptation to hypoxia. ***Mol Cell***. 2011; 44(4):532-44. PMCID: PMC3360955.
- Scortegagna M, Kim H, Li JL, Yao H, Brill LM, Han J, Lau E, Bowtell D, Haddad G, Kaufman RJ, Ronai ZA. Fine tuning of the UPR by the ubiquitin ligases Siah1/2***. PLoS Genet***. 2014; 10(5):e1004348. PMCID: PMC4014425.
- Lau E, Feng Y, Claps G, Fukuda MN, Perlina A, Donn D, Jilaveanu L, Kluger H, Freeze HH, Ronai ZA. The transcription factor ATF2 promotes melanoma metastasis by suppressing protein fucosylation. ***Sci Signal***. 2015; 8(406):ra124. PMCID: PMC4818095.
- Claps G, Cheli Y, Zhang T, Scortegagna M, Lau E, Kim H, Qi J, Li JL, James B, Dzung A, Levesque MP, Dummer R, Hayward NK, Bosenberg M, Brown KM, Ronai ZA. A transcriptionally inactive ATF2 variant drives melanomagenesis. ***Cell Rep***. 2016; 15(9):1884-92. PMCID: PMC4889472.

Ubiquitin ligases and kinases in cancer (development, therapy, immunity). *Siah2 in melanoma and aggressive prostate cancer, RNF5 in the control of glutamine carrier proteins in BCa, PDK1 role in melanoma*

- Qi J, Nakayama K, Gaitonde S, Goydos JS, Krajewski S, Eroshkin A, Bar-Sagi D, Bowtell D, Ronai Z. The ubiquitin ligase Siah2 regulates tumorigenesis and metastasis by HIF-dependent and -independent pathways. ***Proc Natl Acad Sci USA***. 2008; 105(43):16713-8. PMCID: PMC2575485.
- Qi J, Nakayama K, Cardiff RD, Borowsky AD, Kaul K, Williams R, Krajewski S, Mercola D, Carpenter PM, Bowtell D, Ronai ZA. Siah2-dependent concerted activity of HIF and FoxA2 regulates formation of neuroendocrine phenotype and neuroendocrine prostate tumors. ***Cancer Cell***. 2010; 18(1):23-38. PMCID: PMC2919332.
- Qi J, Tripathi M, Mishra R, Sahgal N, Fazli L, Ettinger S, Placzek WJ, Claps G, Chung LW, Bowtell D, Gleave M, Bhowmick N, Ronai ZA. The E3 ubiquitin ligase Siah2 contributes to castration-resistant prostate cancer by regulation of androgen receptor transcriptional activity. ***Cancer Cell***. 2013; 23(3):332-46. PMCID: PMC3750989.
- Scortegagna M, Ruller C, Feng Y, Lazova R, Kluger H, Li JL, De SK, Rickert R, Pellecchia M, Bosenberg M, Ronai ZA. Genetic inactivation or pharmacological inhibition of Pdk1 delays development and inhibits metastasis of $Braf^{V600E}$::$Pten^{-/-}$ melanoma. ***Oncogene***. 2014; 33(34):4330-9. PMCID: PMC3955742.
- Jeon YJ, Khelifa S, Ratnikov B, Scott DA, Feng Y, Parisi F, Ruller C, Lau E, Kim H, Brill LM, Jiang T, Rimm DL, Cardiff RD, Mills GB, Smith JW, Osterman AL, Kluger Y, Ronai ZA. Regulation of glutamine carrier proteins by RNF5 determines breast cancer response to ER stress-inducing chemotherapies. ***Cancer Cell***. 2015; 27(3):354-69. PMCID: PMC4356903.

Ubiquitin ligases in anti-tumor immunity and autoimmunity*. Demonstrated that RNF5 defines the gut microbiota's ability to induce anti-tumor immunity and tumor inhibition while the same ubiquitin ligase defines susceptibility to intestinal inflammation (IBD like phenotypes).*

- Fujita Y, Khateb A, Li Y, Tinoco R, Zhang T, Bar-Yoseph H, Tam MA, Chowers Y, Sabo E, Gerassy-Vainberg S, Starosvetsky E, James B, Brown K, Shen-Orr SS, Bradley LM, Tessier PA, Ronai ZA. Regulation of S100A8 stability by RNF5 in intestinal epithelial cells determines intestinal inflammation and severity of colitis. ***Cell Rep***. 2018; 24(12):3296-3311.e6. PMCID: PMC6185744.
- Li Y, Elmén L, Segota I, Xian Y, Tinoco R, Feng Y, Fujita Y, Segura Muñoz RR, Schmaltz R, Bradley LM, Ramer-Tait A, Zarecki R, Long T, Peterson SN, Ronai ZA. Prebiotic-Induced Anti-tumor Immunity Attenuates Tumor Growth. ***Cell Rep***. 2020 Feb 11;30(6):1753-1766. PMCID: PMC7053418.
- Scortegagna M, Hockemeyer K, Dolgalev I, Poźniak J, Rambow F, Li Y, Feng Y, Tinoco R, Otero DC, Zhang T, Brown K, Bosenberg M, Bradley LM, Marine JC, Aifantis I, Ronai ZA. Siah2 control of T-regulatory cells limits anti-tumor immunity. ***Nat Commun***. 2020 Jan 7;11(1):99. PMCID: PMC6946684.
- Kim H, Kim H, Feng Y, Li Y, Tamiya H, Tocci S, Ronai ZA. PRMT5 control of cGAS/STING and NLRC5 pathways defines melanoma response to antitumor immunity. ***Sci Transl Med.*** 2020; 12(551):eaaz5683. PMCID: PMC7508354.

Recent reviews related to our fields of interest (out of over 50):

- Adaptive stress responses during tumor metastasis and dormancy. ***Trends Cancer***. 2016 Aug;2(8):429-442. PMCID: PMC5114008.
- Precision oncology: the road ahead. ***Trends Mol Med***. 2017; 23(10):874-898. PMCID: PMC5718207.

- Ubiquitin ligases in oncogenic transformation and cancer therapy. ***Nat Rev Cancer***. 2018; 18(2):69-88. PMCID: PMC6054770.
- Ubiquitin ligases in cancer immunotherapy - balancing antitumor and autoimmunity. ***Trends Mol Med***. 2019; 25(5):428-443. PMCID: PMC6488401.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/ze'ev.ronai.1/bibliography/47757767/public/

Lab web page – www.ronailab.net

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

Ongoing Research Support

5 R35 CA197465-05 (PI: Ronai, Z.) 02/02/2016 – 01/31/2023
NIH/NCI
Rewired Signaling at the Nexus Melanoma Metastasis and Resistance
Goal: To establish novel mechanisms underlying tumor plasticity, enabling the development of novel agents for predicting, monitoring, and preventing tumor metastasis and resistance.

5 P01 CA128814-10 05/05/2016 – 04/30/2021
NIH/NCI
PI Project 1: Ronai, Z.
PI Core A: Ronai, Z.
ER Stress and Mitochondrial Biogenesis in Melanoma
Goals: To identify new therapeutic strategies for overcoming drug resistance and metastatic disease in melanoma. CO-PI, Drs. Karin (UCSD), Bosenberg (Yale), Kelly (Penn), Goding (Oxford), Koumenis (Penn).

5 R01 CA202021-05 (PI: Ronai, Z.) 07/01/2016 – 06/30/2021
NIH/NCI
Control of Protein Synthesis by the UPS Under Stress
Goal: The major goal of this project is to establish the importance and significance of select UPS components in a novel regulatory network that controls protein synthesis during cellular stress. Collaborators: Drs. Sonenberg (McGill) and Topisirovic (Lady Davis).

T30IP0941 (PI: Ronai, Z) 10/22/2019 – 10/21/2021
TRDRP
Role of the E3 ubiquitin ligase RNF125 in pancreatic cancer
Goal: define the role of RNF125 in pancreatic cancer development and progression.

Completed Research Support
W81XWH-18-1-0216 (PI: Ronai, Z) 08/15/2018 – 08/14/2020
DOD
Siah2 Ubiquitin Ligase in Immune Checkpoint and Melanomagenesis
Goal: characterize the regulation of anti-tumor immunity by the ubiquitin ligase Siah2, using melanoma models.