## 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: **Ronai, Ze'ev**

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

POSITION TITLE: Professor and Director, NCI designated Cancer Center @ SBP

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. | 06/1980 | Biology |
| The Hebrew University, Jerusalem, Israel | M.S. | 07/1982 | Microbiology |
| The Hebrew University, Jerusalem, Israel | Ph.D. | 11/1985 | Immunobiology |
| Columbia University, New York, New York | Postdoc | 12/1988 | Molecular Biology |

### A. Personal Statement

My passion for science is reflected in my dedication to solving critical unmet clinical problems in cancer, with the focus of my research on epigenetic mechanisms that underlie tumor development, progression, and resistance. Our studies often provided new fundamental understanding for rewired signal transduction pathways in cancer, focusing on epigenetic regulators, including ubiquitin ligases, resulting in novel paradigms. In addition to the privilege of serving as a cancer researcher, I have had several administrative duties, including the establishment of the Signal Transduction Program, serving as Associate Director / Deputy Director to NCI Cancer Center, Scientific Director at Sanford Burnham Prebys Medical Discovery Institute (SBP) La Jolla, and over the past few years, parallel to serving as Chief Scientific Advisor at SBP, I have established a new cancer center at the Technion, in Israel (Technion Integrated Cancer Center, with the Nobel Laureate Aaron Ciechanover). Currently, I serve as the Director of the NCI-designated Cancer Center at SBP.

I have initiated and led several large grant initiatives, led the SAC for the Melanoma Research Foundation, and the DOD melanoma parent vision committee. In addition to serving on several editorial boards, I served as EiC for Pigment Cell Melanoma Research, the formal journal for the melanoma society. Among notable scientific contributions was the development of sensitive PCR enabling the detection of mutant Ras oncogene in normal-appearing tissues, defining the early days of personalized 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.

**Ongoing and pending projects include:**

P30 CA030199, Ronai, Z. (PI)
05/29/2022 – 04/30/2027
*Cancer Center Support Grant (CCSG)*

R35 CA197465, Ronai, Z. (PI)
02/02/2016 – 01/31/2023
*Rewired Signaling at the Nexus Melanoma Metastasis and Resistance*

R01 CA266973, Ronai, Z. Olson, S (MPI)
07/01/2022 – 06/31/2027
*GCDH Addiction in Melanoma*

**B. Positions, Scientific Appointments, and Honors**

| | |
|---|---|
| 2021 – Present | Director, NCI Cancer Center, SBP Medical Discovery Inst., La Jolla, CA. |
| 2021 – Present | Professor, Aging Immuno-oncology Program, SBP Medical Discovery Inst., La Jolla, CA. |
| 2021 - 2023 | Chair, DOD (CDMRP) programmatic vision committee in melanoma. |
| 2016 – 2020 | Chief Scientific Advisor, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA. |
| 2016 – 2018 | Professor & Co-Director, Technion Integrated Cancer Center, Technion, Haifa, Israel. |
| 2013 – 2016 | Scientific Director, Sanford-Burnham Medical Research Institute, La Jolla, CA. |
| 2013 – 2020 | Professor, Tumor Initiation and Maintenance Program, SBMRI, La Jolla, CA. |
| 2008 – 2014 | Associate/Deputy Director, NCI Cancer Center, SBMRI, La Jolla, CA. |
| 2005 – 2016 | Adjunct Professor, Molecular Pathology Program, UC San Diego, La Jolla, CA. |
| 2004 – 2013 | Director, and Professor, Signal Transduction Prog, Sanford-Burnham Med Res Inst, CA. |
| 1993 – 1998 | Consultant, Department of Medicine, Memorial Sloan Kettering, New York, NY. |
| 1989 – 1997 | Assistant/Associate Prof. Depts Microbiology Pathology, NY Med College, Valhalla, NY. |
| 1988 – 1998 | Head, Molecular Carcinogenesis Program, American Health Foundation. |
| 1985 – 1989 | Postdoctoral Fellow, Columbia University, NY, Mentor I.B. Weinstein. |
| 1982 – 1985 | Ph.D., Lautenberg Center, Hebrew University, Jerusalem, Israel. |
| 1999 – 2005 | Professor, Ruttenberg Cancer Center, MSSM, New York, NY. |
| 1997 – 1999 | Associate Professor, Ruttenberg Cancer Center, Mount Sinai School of Medicine, NY. |

**Professional Activities:**

***NIH grant review***: *2021- 2023, DOD (CDMRP) melanoma vision committee;* 2018-2020 – DOD CDMRP vision committee; 2012–present Ad Hoc NCI study sections CAMP, TCB, OIA/R35, and others; 2012 NCI Provocative Questions; 2007–2009 NIH TPM Study Section; 2001 NIH Review for PPG on Melanoma Biology; 1996–2001 Member of NCI Chemical Pathology Study Section; 1995 NIH Review Committee for Program Project on Radiation Biology; 1995–1997 NCI Multidisciplinary Special Emphasis Study Section; 1994–1999 Member Cancer Study Section Tobacco Research Program, UCSF; 1991 NIH committee for RFA in Radiation Biology.

***Scientific Advisory Boards***: Co-leader of the SAC for Melanoma Research Foundation (MRF); P01, University of Arizona, Tucson; P01, Wistar Institute, Philadelphia; SPORE, University of Colorado, Denver, Cancer Center, MGH, Boston. ***Conference Organization*****:** 2016 Melanoma workshop, Israel; 2015 Melanoma workshop Iceland; 2015, Ubiquitin Workshop, Southern China; 2007 Co-organizer International Melanoma Conference; 2004, 2006, 2010 Co-organizer, Ubiquitin Workshop, Hebrew University, Jerusalem; 2000 Co-Chair, NIH workshop on Melanoma; 1996 Organizing Committee, Cancer & Biotechnology, Nice, France; Organizing committee, 4th International Cancer Biotech., Geneva, Switzerland; 1994 Chair, Int. Cell Diff. Conf Hiroshima, Japan.

***Editorial***: 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;* 2007–2009 Executive Editor *Pigment Cell and Melanoma Research;* 2007–2010 Associate Editor *Cancer Research*; 2002–present *Molecular and Cellular Biology*; 2002–2007 *Journal of Biological Chemistry*; 2002–present *Cancer Biology and Therapy*; 2001–present *Molecular Carcinogenesis*; 1997–2001 *Cancer Prevention and Detection*; 1999–2002 Associate Editor *Clinical Cancer Research*;1996–98 and 2001–2003 *Carcinogenesis*.

**Awards and Honors:**

| | |
|---|---|
| 2023 | NCI Director's Ground Rounds presentation |
| 2023 | Keynote speaker, the annual SMR meeting, Philadelphia. |
| 2022 | Osher Lifelong Learning Institute at UCSD. |
| 2021,2023 | AACI, NCI designated Cancer Center @ SBP presentation |
| 2020 | Keynote speaker, Cancer Biology & Signaling Program Retreat, UCSD, La Jolla, CA. |
| 2020 | Distinguished Scientist Seminar, University of Maryland, MD. |
| 2019 | Keynote speaker, C3 (UCSD; Salk; SBP) cancer centers symposia. |
| 2016 | Society Melanoma Research, Lifetime Achievement Award, Boston, MA. |
| 2016 | Frontiers in Cancer Research at the Nobel Forum, Karolinska Institutet, Stockholm, Sweden. |
| 2014 | UCI Cancer Center Retreat, Keynote speaker. |
| 2013 | UCSD Cancer Center Director's Seminar Series, speaker. |

2012 NCI Director Lecture Series.
2008 Keynote speaker, Melanoma Symposium, Penn State University.
2004 Karolinska Nobel Conference on Hypoxia, Stockholm, Sweden.
2002, 2005 Banbury Conference CSH, Melanoma biology.
2001 Karolinska Nobel Conference on Ubiquitin, Stockholm, Sweden.
2000 Dean lecture series – Mount Sinai School of Medicine.
1995 Princess Takamatsu Symposium, Tokyo; Hiroshima Cancer Symposium.
1992 JPCR Fellowship from National Cancer Center, Tokyo.
1984 Awarded the Golda Meir Fellowship.
1982 Prize from the Hebrew University for MS. Outstanding Thesis.

**C. Contributions to Science** (over 28,000 citations; H-index >95; i10 index >225; >300 publications)

**Among the Significant discoveries from my lab are:**

***Rewired signaling in cancer****. Demonstrated cross talk between ERK and JNK, STAT3 and c-Jun, RACK1 and JNK signaling in melanoma, and rewired metabolic signaling in melanoma.*

- 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.
- Lopez-Bergami P, Huang C, Goydos JS, Yip D, Bar-Eli M, Herlyn M, Smalley KS, Mahale A, Eroshkin A, Aaronson S, Ronai Z. Rewired ERK-JNK signaling pathways in melanoma. ***Cancer Cell****.* 2007; 11(5):447-60. PMC1978100.
- Lau E, Kluger H, Varsano T, Lee K, Scheffler I, Rimm DL, Ideker T, Ronai ZA. PKCε promotes oncogenic functions of ATF2 in the nucleus while blocking its apoptotic function at mitochondria. ***Cell****.* 2012; 148(3):543-55. PMC3615433.
- 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. PMC7307327.

***Ubiquitin ligases control fundamental cellular processes****. The role of Siah2 in hypoxia, in UPR (unfolded protein response), in the control of mitochondrial fission, and the duration of stress signaling (TRAF2/JNK). Discovered the regulation of IκB and β-catenin stability by β-TRCP ubiquitin ligase*

- 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.
- Nakayama K, Frew IJ, Hagensen M, Skals M, Habelhah H, Bhoumik A, Kadoya T, Erdjument-Bromage H, Tempst P, Frappell PB, Bowtell DD, Ronai Z. Siah2 regulates stability of prolyl-hydroxylases, controls HIF1alpha abundance, and modulates physiological responses to hypoxia. ***Cell***. 2004; 117(7):941-52. PMID: 15210114.
- 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. PMC4014425.
- 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. PMC3360955.

***Ubiquitin ligases in cancer development, therapy-resistance.*** *Established the role of Siah2 in: melanoma development and metastasis; development of neuroendocrine prostate cancers; hormone-refractory prostate cancer. Discovered the importance of RNF5 in the control of glutamine carrier proteins, for BCa responsiveness taxenes, basis for clinical trials. RNF125 in melanoma resistance to BRAF inhibitor.*

- 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. 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. PMC3750989.
- 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. PMC4356903.
- 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. doi: 10.1038/s41467-019-13826-7. PMC6946684.

***Ubiquitin ligase in the interplay between autoimmunity and anti-tumor immunity****. 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).*

- 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. PMC6445090.
- 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. 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. PMC7053418.
- 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 8;12(551): eaaz5683. PMC7508354.

***Targeting cancer by novel therapeutics.*** *Targeting the eIF4F – translation initiation complex using SBI-756, provided a new paradigm for cancer treatment, exemplified for melanoma and DLBCL. Targeting ASNS in pancreatic cancer and melanoma, in combination with MEKi, provided the basis for a clinical trial that is ongoing at OHSU. Targeting AML with a low level of RNF5 expression using HDAC inhibitors provides the basis for clinical evaluation currently developed at Scripps.*

- 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. doi: 10.1158/0008-5472.CAN-15-0885. PMC4681635.
- Pathria G, Lee JS, Hasnis E, Tandoc K, Scott DA, Verma S, Feng Y, Larue L, Sahu AD, Topisirovic I, Ruppin E, Ronai ZA**.** Translational reprogramming marks adaptation to asparagine restriction in cancer. ***Nat Cell Biol***. 2019; (12):1590-1603. doi: 10.1038/s41556-019-0415-1. PMC7307327.
- Khateb A, Deshpande A, Feng Y, Finlay D, Lee JS, Lazar I, Fabre B, Li Y, Fujita Y, Zhang T, Yin J, Pass I, Livneh I, Jeremias I, Burian C, Mason JR, Almog R, Horesh N, Ofran Y, Brown K, Vuori K, Jackson M, Ruppin E, Deshpande AJ, Ronai ZA. The ubiquitin ligase RNF5 determines acute myeloid

leukemia growth and susceptibility to histone deacetylase inhibitors. ***Nat Commun***. 2021; 12(1):5397. doi: 10.1038/s41467-021-25664-7. PMC8437979.

- Verma S, Crawford D, Khateb A, Feng Y, Sergienko E, Pathria G, Ma CT, Olson SH, Scott D, Murad R, Ruppin E, Jackson M, Ronai ZA. NRF2 mediates melanoma addiction to GCDH by modulating apoptotic signaling. ***Nat Cell Biol***. 2022; 24(9):1422-1432. doi: 10.1038/s41556-022-00985-x PMC9977532.

**Complete List of Published Work in My Bibliography:**

https://www.ncbi.nlm.nih.gov/sites/myncbi/ze'ev.ronai.1/bibliography/47757767/public/?sort=date&direction=descending

*Lab web page – www.ronailab.net*