BIOGRAPHICAL SKETCH

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NAME: Lior Appelbaum

POSITION TITLE: Professor, Principal Investigator

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
Bar-Ilan University, Israel	B.Sc.	1996-2000	Life Sciences
Bar-Ilan University, Israel	M.Sc.	2000-2001	Molecular Ecology
Bar-Ilan University, Israel	Ph.D.	2001-2005	Neuroendocrinology
Stanford University, USA	Postdoctoral	2005-2010	Molecular Neuroscience

A. Personal Statement

My lab interest is genetic and cellular mechanisms that underline brain function, with a particular focus on neurodevelopmental disorders, evolution and development of the nervous system, sleep and sleep disorders. To address these questions, we integrate cutting-edge genetic engineering, real-time two-photon imaging of single molecules and cells, computational analysis and high-resolution video tracking of behavior in live zebrafish, reef fish and cnidarians. The zebrafish offers a powerful vertebrate model due to its evolutionarily conserved brain organization, optical transparency, and unique suitability for live imaging and high-throughput genetic and pharmacological approaches. To model human brain disorders, we generate and study zebrafish models, probing gene and circuit function through loss- and gain-of-function strategies including CRISPR/Cas9-based genome editing, genetic silencing, targeted ablation of neuronal populations, transposon-mediated transgenesis, pharmacological manipulation, and optogenetics. In addition to basic and translational research, I routinely teach basic and advanced undergraduate and graduate courses such as the introduction to endocrinology course. A key aspect of our research program is mentoring junior scientists, and my laboratory has a successful record of training undergraduate, master and doctoral students as well as postdoctoral fellows, three of them became independent principal investigators.

B. Positions, Scientific Appointments, and Honors

POSITIONS

2019-present Full Professor, Bar Ilan University, Israel.
2024-2025 Visiting Professor, University of Queensland, Australia.
2015-2019 Associate Professor, Bar Ilan University, Israel.
2016-2017 Visiting Professor, Stanford University, Palo Alto, CA, USA.
2010-2015 Assistant Professor, Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel.
2005-2006 Researcher in the Center for Marine Studies, University of Queensland, Australia.
2004 Volunteer adjunct technician in the National Institute of Child Health & Human Development, NIH, USA.
2003 Volunteer adjunct technician in the National Institute of Mental Health, NIH, USA.

C. Contributions to Science

1. Novel cellular function for sleep, characterization of sleep in zebrafish, dissecting hypothalamic neuronal network, and establishing zebrafish models for sleep disorders. We defined sleep in single

neurons, discovered new nuclear role for sleep, cloned sleep genes, identified sleep regulating neuronal circuits and generated transgenic and mutant fish models for insomnia and narcolepsy.

1. Zada D, Sela Y, Matosevich N, Monsonego A, Lerer-Goldshtein T, Nir Y, and **Appelbaum L** (2021) Parp1 promotes sleep, which enhances DNA repair in neurons. ***Molecular Cell***. 81:4979-4993.
   *This paper was previewed in:
   Zlotorynski E, (2021) Sleep tight thanks to Parp1. *Nat Rev Mol Cell Biol*. 23:1
   Lewis S (2021) DNA damage drives sleep. *Nature Neuroscience*. https://doi.org/10.1038/s41583-021-00550-9.
   Schibler U (2021) PARP-1 drives slumber: A reciprocal relationship between sleep homeostasis and DNA damage repair. *Molecular Cell*. 81:4958-4959.
2. Zada D, Bronshtein I, Lerer-Goldshtein T, Garini Y, **Appelbaum L** (2019) Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. ***Nature Communications***. 10:895.
   *This paper was highlighted in over 70 news outlets (including "The scientific breakthrough of the month", *National Geographic*), recommended in F1000Prime, accessed by more than 48,000 viewers and ranked in 99th percentile in Altmetric (Score: 1051).
3. Yelin-Bekerman L, Elbaz I, Diber A, Dahary D, Gibbs-Bar L, Lerer-Goldshtein T, **Appelbaum L** (2015) Transcriptional profiling of hypocretin neurons identifies the sleep regulator Kcnh4a. ***eLife***. 4:e08638.
   This paper was highlighted in *eLife* insight. Giardino and de Lecea (2015) Transcriptomics: Resting easy with a sleep regulator. *eLife* 4. pii: e12093.
4. Elbaz I, Yelin-Bekerman L, Nicenboim J, Vatine G, and **Appelbaum L** (2012) Genetic ablation of hypocretin neurons alters behavioral state transitions in zebrafish. ***Journal of Neuroscience***. 32:12961-12972.

2. Sleep-dependent structural synaptic plasticity and activity of neuronal circuits in live animal. We established synaptic markers and neuronal sensors and used live two-photon imaging to show how the circadian clock and sleep regulate structural synaptic plasticity and how brain cells interact in live animal.

1. Sagi D, Tibi T, Admati I, Lerer-Goldshtein T, Hochgerner H, Zeisel A, **Appelbaum L** (2024) Single-cell profiling uncovers evolutionary divergence of Hypocretin/Orexin neuronal subpopulations. ***Journal of Neuroscience***. 44:e0095242024.
2. Elbaz I, Zada D, Tovin A, Braun T, Lerer-Goldshtein T, Wang G, Mourrain P, **Appelbaum L** (2016). Sleep-Dependent Structural Synaptic Plasticity of Inhibitory Synapses in the Dendrites of Hypocretin/Orexin Neurons. ***Molecular Neurobiology***. doi:10.1007/s12035-016-0175-x.
3. Elbaz I, Lerer-Goldshtein T, Okamoto H and **Appelbaum L** (2015) Reduced synaptic density and deficient locomotor response in neuronal activity-regulated pentraxin 2a mutant zebrafish. **FASEB Journal**. 29:1220-34.
4. **Appelbaum L**, Wang G, Yokogawa T, Skariah G, Smith SJ, Mourrain P and Mignot E (2010) Circadian and homeostatic regulation of structural synaptic plasticity in hypocretin neurons. ***Neuron***. 68:87-98 (cover)*. PMCID: PMC2969179.
   *This paper was highlighted in *Nature* (2010), community choice: the most viewed paper in science, Neuroscience: Brain connections have rhythm. *Nature*. 468: 349.

3. Discovery of the molecular mechanisms and evaluating potential treatments for neurodevelopmental disorders. We linked RNA editing in synaptic genes with increased synapse number and hyperactivity of zebrafish model for fragile X syndrome. In addition, we established a zebrafish model for the psychomotor retardation Allan-Herndon-Dudley syndrome (AHDS) that demonstrate endocrinological and neurological deficiencies, which are similar to human patients. This model zebrafish was used to test potential pharmacological treatments and BBB-targeted gene therapy, which enhanced myelination and recovered other neurological deficiencies. Drugs that showed positive results in the zebrafish model are currently used in clinical trials and the BBB-targeted gene therapy is tested in mice.

1. Uribe-Arias A, Rozenblat R, Vinepinsky E, Marachlian E, Kulkarni A, Zada D, Privat M, Topsakalian D, Charpy S, Candat V, Nourin S, **Appelbaum L**, Sumbre G (2023) Radial astrocyte synchronization modulates the visual system during behavioral-state transitions. ***Neuron***. 111:4040-4057.

2. Wasserman-Bartov T, Admati I, Lebenthal-Loinger I, Sharabany J, Lerer-Goldshtein T, and **Appelbaum L** (2022) Tsh induces Agrp1 neuron proliferation in Oatp1c1 deficient zebrafish. ***Journal of Neuroscience***. 42:8214-8224.
3. Admati I, Wasserman-Bartov T, Tovin A, Rozenblat R, Rozenblat R, Blitz E, Zada D, Lerer-Goldshtein T, **Appelbaum L** (2019) Neural alterations and hyperactivity of the hypothalamic–pituitary–thyroid axis in Oatp1c1-deficiency. ***Thyroid***. 30:161-174.
4. Zada D, Tovin A, Lerer-Goldshtein T, **Appelbaum L** (2016). Pharmacological and BBB-targeted genetic therapies for thyroid hormone-dependent hypomyelination. ***Disease Models & Mechanisms***. 9:1339-1348.
5. Shamay-Ramot A, Khermesh K, Porath HT, Pinto Y, Wachtel C, Barak M, Lerer-Goldshtein T, Levanon EY and **Appelbaum L** (2015) Impaired neural circuit formation and augmented RNA editing enzyme activity in fragile X syndrome. ***PLoS Genetics***. 11:e1005702.

4. Elucidating the mechanism of circadian rhythms, neural evolution and sleep in marine invertebrates. We provide the molecular neurobiology expertise in several collaborative projects that study the nervous system and circadian rhythms of marine invertebrates.

1. Aguillon R, Harduf A, Sagi D, Simon-Blecher N, Levy O, **Appelbaum L** (2026) DNA damage modulates sleep drive in basal cnidarians with divergent chronotypes. ***Nature Communications***. 17:3. doi: 10.1038/s41467-025-67400-5
2. Surm JM, Birch S, Macrander J, Jaimes-Becerra A, Fridrich A, Aharoni R, Rozenblat R, Sharabany J, **Appelbaum L**, Reitzel AM, Moran Y (2024) Venom tradeoff shapes interspecific interactions, physiology and reproduction. ***Science Advances***. 10:eadk3870
3. Aguillon R, Rinsky M, Simon-Blecher N, Doniger T, **Appelbaum** L, Levy O (2024) CLOCK evolved in cnidaria to synchronize internal rhythms with circadian environmental cues. ***eLife***. https://doi.org/10.7554/eLife.89499.2.
4. Levy O, **Appelbaum L**, Leggat W, Gothlif Y, Hayward DC, Miller DJ and Hoegh-Guldberg O (2007) Light-responsive cryptochromes from the simplest marine eumetazoan animals. ***Science***. 318: 467-470.

5. Circadian rhythms in fish. We characterized the mechanisms that regulate circadian outputs and brain connectomics.

1. Jaggard J, Lloyd E, Yuiska A, Patch A, Fily Y, Kowalko JE, **Appelbaum L**, Duboue ER, Keene AC. (2020) Cavefish brain atlases reveal functional and anatomical convergence across independently evolved populations. ***Science Advances***. doi: 10.1126/sciadv.aba3126.
2. Dvir H, Elbaz I, Havlin S, **Appelbaum L**, Ivanov PC, Bartsch RP (2018) Neuronal noise as an origin of sleep arousals and its role in sudden infant death syndrome. ***Science Advances***. 4:eaar6277.
3. **Appelbaum L**, Wang G, Maro G, Mori R, Tovin A, Marin W, Yokogawa Y, Kawakami K, Smith SJ, Gothilf Y, Mignot EM and Mourrain P (2009). Sleep/wake regulation and hypocretin-melatonin interaction in zebrafish. ***Proceedings of the National Academy of Sciences U S A***. 106:21942-21947 (track II). PMCID: PMC2799794.
4. Vatine G, Vallone D, **Appelbaum L**, Mracek P, Ben-Moshe Z, Lahiri K, Gothilf Y and Foulkes NS (2009) Light directs zebrafish period2 expression via conserved D and E boxes. ***PLoS Biology***. 7:e1000223.