

Brain Medicine

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INNOVATORS & IDEAS: RESEARCH LEADER

Illana Gozes: From the pivotal discovery of activity-dependent neuroprotective protein (ADNP) through its investigational drug davunetide: brain molecular medicine providing hope for autism, schizophrenia, and Alzheimer's disease

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Professor Illana Gozes, Ph.D., is a faculty member at Tel Aviv University. Formerly holding the Lily and Avraham Gildor Chair for the Investigation of Growth Factors, she now directs the Dr. Diana and Zelma Elton Laboratory for Molecular Neuroendocrinology. A world-renowned neurochemist, Professor Gozes currently serves as the President of the European Society for Neurochemistry and Vice President of Drug Development at ExoNavis Therapeutics Ltd. Her groundbreaking research began in the late 1970s and early 1980s when she discovered multiple tubulin forms within a single neuron. She demonstrated that these forms evolve with brain development, play a crucial role in synapse formation, and can be identified using monoclonal tubulin antibodies. At the forefront of molecular neuroscience in the 1980s, Professor Gozes became the first to clone the gene encoding vasoactive intestinal peptide (VIP), a key regulatory neuropeptide in the brain. Her research revealed increased VIP expression during synapse formation. In her quest to identify proteins activated by VIP and facilitate neuro-glial interaction, the Gozes laboratory discovered and cloned a novel protein: activity-dependent neuroprotective protein (ADNP). Subsequent research established ADNP's essential role in brain formation and function. Through a series of highly cited articles, Professor Gozes demonstrated that ADNP regulates thousands of essential genes during brain development in a sex-dependent manner and associates with an intricate array of vital proteins. She uncovered ADNP's key role in autophagy and schizophrenia, revealed a fundamental shared mechanism in autism involving critical binding of ADNP with SHANK3 and actin, and showed ADNP's regulation of microtubule dynamics and Tau interaction, which protects against tauopathy. Furthermore, she discovered somatic mutations in ADNP and related genes in Alzheimer's disease, paralleling tauopathy. Her pioneering work on ADNP-deficient mouse models predicted the ADNP syndrome, an autistic/intellectual disability syndrome driven by de novo mutations in ADNP and presenting with tauopathy. Professor Gozes took a reductionist approach to discover an active site in ADNP, leading to the development of the investigational drug davunetide (NAP). This compound has shown promise in protecting against ADNP deficiency/mutations in animal models and in clinical trials. It has been tested in women suffering from progressive supranuclear palsy (PSP), a pure tauopathy, and in individuals with prodromal Alzheimer's disease, demonstrating effects in a sex-dependent manner. Further promise was shown in schizophrenia patients, suggesting improvement in real-world problem solving and task performance. We are honored that Professor Gozes has agreed to share her life's journey with our readers in this Genomic Press Interview.



Figure 1. Illana Gozes, PhD, Tel Aviv University, Israel.

Part 1: Illana Gozes – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was born and raised in Jerusalem, Israel, my late grandfather (Menahem Mendel Haltovsky) was a medic with a catching love and passion for providing help to his patients. In primary school, equipped with a microscope and books about renowned scientists, I was very interested in finding out how things worked. I liked mathematics and took it as a major at my prestigious high school. However, my late father (Isac Allon), who was a civil engineer, convinced me that solving nature needs more than mathematics. The heart of Jerusalem at that time was the Hebrew University and the Parliament House. I was not drawn to politics but was inspired by the intellectual spiritual nature of the beautiful city of Jerusalem and admired academics in the field of biology and medicine. I chose Tel Aviv University, then a young and aspiring university close to the tranquil Mediterranean beach, for my under graduate studies and loved every moment of my studies. At the time of my graduation, the Weizmann Institute of Science started a direct Ph.D. program for the best students in biology country-wide. I was amongst the chosen 16 students and neurochemistry became my life passion, the molecular understanding of the brain toward helping humanity to fight brain diseases.

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We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

As a young undergraduate and graduate student, I was extremely interested in my experiments and my results, always enchanted by new techniques and new problems. It became clear to me that it is of the utmost importance to share one's knowledge, either in lectures or in writing. My first paper, published in the Proceedings of the National Academy of Science (USA) entitled: "Translation in vitro of rat brain messenger RNA coding for tubulin and actin" combined both the strive to understand the intricate function of the brain at the molecular level and the grasp of the importance of sharing knowledge to move forward. As such, I was fortunate to participate in the birth of the then a new field, molecular neuroscience. In one of my papers, accepted w/o any changes, we discovered tubulin and actin synthesis in brain cell nuclei, a very new and exciting finding back then. I think that my persistence and hard work ethics channeled me toward leadership and responsibilities coupled with the passion for sharing and openness to collaborative work. Some of my best friends are my work colleagues, and my lab personnel represent my extended family members.

Please share with us what initially piqued your interest in your favorite research or professional focus area

Marie Curie findings, the discovery of the DNA structure, the double helix, the discovery of the need for sterilization, and my first lecture abroad at the Laboratory of Professor Rita Levi Montalcini in Rome, all crystallized my passion for molecular neuroscience. Our cloning of the VIP gene and developing the first transgenic mouse model for VIP, showing learning deficiencies further led me to new discoveries. A most appropriate example, is our identification of ADNP and our investigational drug, davunetide, from gene to behavior and to clinical development. In the early 1980's, I named one of my first grant proposal "From Gene to Behavior" and was awarded for it, by the President of the State of Israel, the first Bergmann Memorial Award for the best grant proposal amongst the US-Israel Binational Science Foundation young applicants.

What impact do you hope to achieve in your field by focusing on specific research topics?

I hope to be able to further understand the mechanism of brain development and aging, leading to better insights on brain diseases, which will allow for better diagnostic measures. I am proud of my work on oral microbiota signatures in post-traumatic stress disorder (PTSD) veterans, published in *Molecular Psychiatry* (2022), with findings complementing discoveries made by the team with Julio Licinio and colleagues in China in the laboratory setting, describing the biogeography of the large intestinal mucosal and luminal microbiome in cynomolgus macaques with depressive-like behavior, originally published in *Molecular Psychiatry* (2021). I further connected microbiota signatures to the autistic/intellectual disabilities ADNP syndrome by in depth characterization of my genetically engineered and genome edited mouse models, toward better diagnosis and most importantly better therapeutics. Focusing on therapeutics, I strive to bring our ADNP-derived investigational drug, davunetide and related compounds providing neuroprotection to affected individuals, turning deep understanding of molecular brain function to medical/societal impact. Here, a major concentrating effort is made on ADNP syndrome children, first collected as a group of 10 children led by Belgian and US scientists and defined as a syndrome, driving increased excellent interest in ADNP and beyond.

Please tell us more about your current scholarly focal points within your chosen field of science

I am very intrigued by the similarities between delayed/aberrant brain development, as in the case of the ADNP syndrome as well as tubulinopathies, and neuropsychiatric diseases like schizophrenia associated with microtubule dysfunction and neurodegenerative diseases with an underlying tauopathy. My first love in science was the protein tubulin and my continuous quest for the understanding of the brain led me to discover a new microtubule – interacting protein, ADNP. I focus on better

understanding of ADNP in the realm of brain development and aging with great interest in sex differences, given my recent findings on unexpected gender differences in progressive supranuclear palsy revealing efficacy for davunetide in women (*Translational Psychiatry*, 2023) and sex-dependent boosting of memory in prodromal Alzheimer's disease (*Translational Psychiatry*, 2024).

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

I engulf myself with work, making precise plans, but open for changes depending on findings. I cherish my dedicated students and collaborators, always striving to work with the best of the best. I have learnt early on from my PhD mentor the late Uriel (Uri) Littauer to share my findings in scholarly publications, which I continued on doing with my postdoctoral fellow mentor, the 2021 Brain Prize winner, Michael (Mike) Moskowitz at MIT who gave me complete freedom to work, collaborate and publish coupled with students, postdoctoral fellows and a technician. For example, Gozes and Sweadner, Multiple tubulin forms are expressed by a single neurone (*Nature*, 1981), & Gozes and Barnstable, Monoclonal antibodies that recognize discrete forms of tubulin (*Proc Natl Acad Sci USA*, 1982). The head of the MIT section at that time, Richard Wurtman passed away recently and together with my recent MSc graduate Yael Toren (his granddaughter), we dedicated one of my latest papers to his memory: Sex-Specific ADNP/NAP (Davunetide) Regulation of Cocaine-Induced Plasticity (*J Molecular Neuroscience*, 2024).

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I think science has no borders, the passion for knowledge and communication brings people together. I enjoy promoting the young and as such, in my capacity as the President of the Israel Society for Neuroscience (2008–2010) I strived to establish the Israel Brain Bee Competition, I set up the Tel Aviv Chapter of the Society for Neuroscience (US) and later founded the Israel Brain Bee initially together with Dr. Tal Iram, the Davidson Institute at the Weizmann Institute of Science and the Youth University at Tel Aviv University. The competition is now running with the support of the Israel Ministry of Education. In the alphabetic organization of the competition, Israel sits side by side with Iran and Italy. These young high school students are equally interested in the brain, I wish for them to inherit a peaceful world.

What do you most enjoy in your capacity as an academic or research leader?

Working and solving problems (I wish I could solve more), publishing and having my work acknowledged and appreciated by others, such Douglas (Doug) Brenneman who was indispensable in our discoveries of activity-dependent neurotrophic factor (ADNF) and later ADNP and Mati Fridkin, my initial VIP collaborator as well as Julio Licinio, inviting my interview, appreciating my works for publication and citing them in his review: "Advances in autism research, 2021: continuing to decipher the secrets of autism". I enjoy writing and interacting with brilliant fellow scientists, I feel science has no age differences. It keeps us young and always striving to be better.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I love spending time with my family, my husband, Yehoshua, our daughter, Adi, her husband Amir, and our three gifted grandchildren, Tom, Emma and Daniel. I love to watch all of them grow and thrive, playing chess, much better than me, solving math and logical problems and just loving them. I am extremely fortunate and proud to have them.

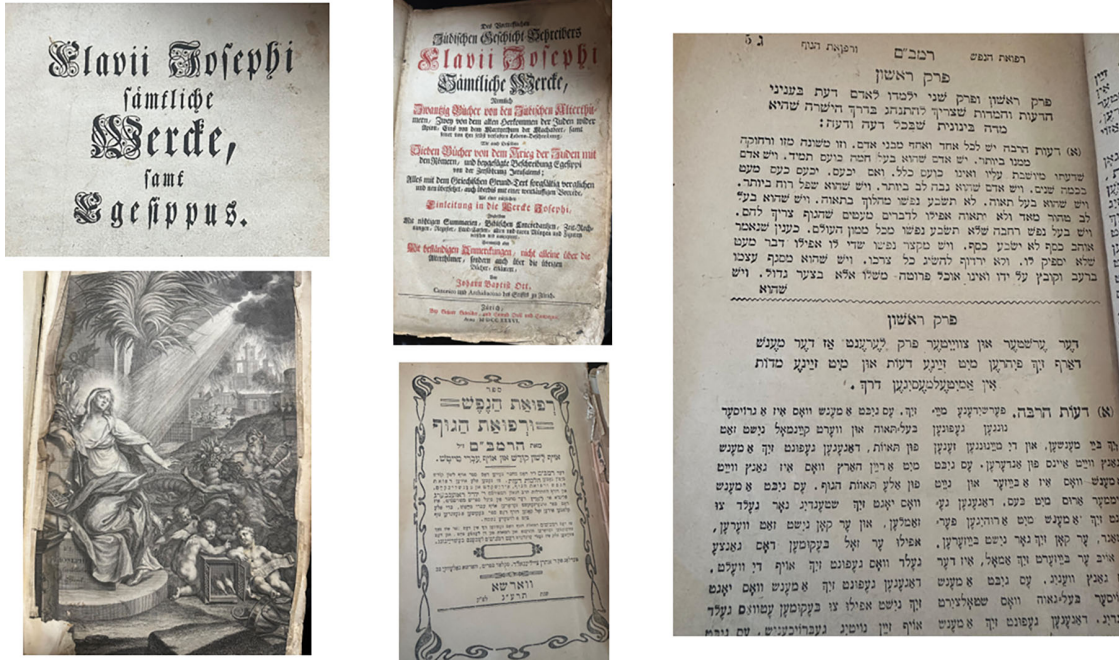


Figure 2. Treasured Possessions. Two written pages and a picture from Josephus Flavius book (a collection) as well as the first and second pages of Maimonides – Medicine for the Body and Medicine for the Soul, in Hebrew and Yiddish. The Maimonides book cover page is depicted followed by the first chapter, saying that people, opinionated as they may be, should behave honestly and always strive to find a middle peaceful way.

Part 2: Illana Gozes – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Love your fellow human being as you love yourself.

What is your greatest fear?

If there is a will, there is a way, I do my best to put my fears aside.

Which living person do you most admire?

My family, my daughter, Adi Gozes – Hamenahem, for being there with me.

What is your greatest extravagance?

Traveling to scientific and business meetings, giving plenary talks and receiving medals (Fogarty-Scholar-in-Residence, NIH, USA) and multiple international awards for research achievements.

What are you most proud of?

Receiving the Champion of Hope Award by Global Genes, recommended by the ADNP parents, for my discovery of ADNP and davunetide: my dream is to help this community!

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your greatest regret?

The hatred of neighbors, I wish all the money spent on ammunition will be spent on science, health and peace, I wish I could help world peace. There is a place in the world for everyone.

What is the quality you most admire in people?

Love, intelligence, and honesty.

What is the trait you most dislike in people?

Hate, bigotry, and dishonesty.

What do you consider the most overrated virtue?

Beauty and success, these are traits judged by the eyes of the beholders.

What is your favorite occupation (or activity)?

Working and writing science and seeing family and friends.

Where would you most like to live?

My home is my castle, I love my home in a small town just outside Tel Aviv, where strawberry fields are mixed with friendly small town urban life.

What is your most treasured possession?

I treasure two books: one of them contains Josephus Flavius writings on the history of the Jews; that is my father's family's heirloom, which we estimate to have been printed around 300 hundred years ago. The other volume is my grandfather's used Maimonides – Medical Book, which we know to be over 100 years old (see Figure 2).

When and where were you happiest? And why were so happy then?

At the birth of my only daughter, I cherished the miracle of life.

What is your current state of mind?

Enjoying writing this article and hoping for peace.

What is your most marked characteristic?

The love for work.



Among your talents, which one(s) give(s) you a competitive edge?

Persistence, curiosity, scientific logic as well as long-term memory.

What do you consider your greatest achievement?

The original discovery, cloning and characterization of ADNP and davunetide, which followed on the original cloning of the VIP gene and the discovery of multiple tubulin subunits in the single neurons, in short, discoveries of molecules that make our minds.

If you could change one thing about yourself, what would it be?

To better understand my fellow human beings and strive for friendship.

What do you most value in your friends?

Compassion and intelligence.

Who are your favorite writers?

Rudyard Kipling, Oscar Wilde, George Bernard Show, Lord George Gordon Byron, Robert Frost, and the Israeli poet, Rachel.

Who are your heroes of fiction?

As a child I liked the story of Hans Brinker or The Silver Skates. I equally liked the characters of Little Women, and my heart ached with the story of the Scarlet Letter. I also like the detectives in Agatha Christy novels as well as Sherlock Holmes and Dr. Watson

Who are your heroes in real life?

Except for my family members, students and collaborators mentioned above, my heroes are my generous supporters and believers of my research, Ephraim (Ephi) Gildor, the Elton family, Ronith and Armand Stemmer, Arie Dubson, Chair A.M.N. Foundation, the late Marcel Adams and his son Sylvan, Holly and Jonathan Strelzik as well as Anne and Alex Cohen. In therapeutics development, I cherish my business partners starting from Allon Therapeutics and now ExoNavis Therapeutics Ltd with its excellent staff, led by Gabriel Eldor and Yoram Drucker. As I have had about 100 trainees, I cannot name them all or exhibit favoritism, but I am very proud of their progress and attainment of prominent positions, like chairing universities, companies, and hospital departments. On my mother's side of the family, I am fascinated by my ancestors, Abraham Senior (Segovia

1412–1493) (later named Coronel) a Jewish rabbi who was a leading tax farmer in Spain and had to convert to Christianity in 1492. His descendant, Nachman Nathan Coronel (1810–1890) was a Jerusalemite Jewish scholar building his home in Jerusalem as a young man for his descendants including me.

What aphorism or motto best encapsulates your life philosophy?

- 1] Rudyard Kipling: "If you can keep your head when all about you are losing theirs and blaming it on you..."
- 2] Robert Frost: (a) "Two roads diverged in a yellow wood and I – I took the one less traveled by and that has made all the difference." (b) "The woods are lovely, dark and deep, but I have promises to keep, and miles to go before I sleep..."

Illana Gozes¹

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