**Genomic Psychiatry** 

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### **INNOVATORS & IDEAS: ACADEMIC LEADER**





Figure 1. Yehezkel Ben-Ari, BSc, Docteur ès Sciences, CEO Neurochlore, France (formerly Founder and Director, INMED (Institut de Neurobiologie de la Méditerranée), INSERM (Institut National de la Santé et de la Recherche Médicale).

necessarily shifting you naturally to study brain development. Being directly above a preterm facility further stimulates one's wish to understand what underlies the delivery timing and generates preterm delivery, again, a domain in which we made significant contributions.

#### 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?

I was born in Egypt in a typical Jewish family, migrated to Israel in 1956 (after the Sinai war), and earned a BS in biology at the Hebrew University before migrating to France, where I earned my Doctorate in Science, specifically dedicated to the mechanisms of brain plasticity. I then had two postdocs, at the University of Cambridge (UK) and at McGill

## Yehezkel Ben-Ari: The Neuroarcheology concept: From brain development to predicting, understanding, and treating brain disorders

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Spanning over four decades at France's premier research institutions (CNRS and INSERM), Dr. Yehezkel Ben-Ari's groundbreaking neuroscience research has fundamentally transformed our understanding of brain development through his seminal discovery of the GABA excitatory-to-inhibitory developmental shift, an evolutionary conserved principle later validated across all species from worms to humans. After directing the INSERM unit at Port-Royal Maternity and founding the Mediterranean Institute of Neurobiology (INMED), Ben-Ari's unexpected observation of GABA's paradoxical excitatory role in immature neurons, which he initially set aside for over a year before recognizing its significance earned him prestigious recognitions including the Grand Prix INSERM, the Milken award of the Epilepsy Foundation of America (EFA) and an award from the European Society of Epilepsy. In this Genomic Press Interview, Ben-Ari reflects on his scientific journey, including his transition after French mandatory retirement to founding innovative therapeutic ventures targeting autism spectrum disorders, epilepsy, and brain tumors based on his unifying "Neuroarcheology" concept, proposing that many neurological disorders stem from developmental mechanisms that can be targeted with specific medications like bumetanide, which has shown promising results in clinical trials by modulating chloride transporters. While continuing to teach at the Pasteur Institute's brain development doctoral program, Ben-Ari's career exemplifies how persistence in investigating unexpected observations can lead to transformative discoveries with profound clinical implications, bridging the gap between fundamental neuroscience research and innovative therapeutic applications for previously untreatable neurological conditions.

#### Part 1: Yehezkel Ben-Ari – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science? Being born in Egypt in a Jewish family and raised in a French Christian school, all this in a Muslim country, cures one from readily endorsing dogmas. Furthermore, when migrating to Israel and being directly involved in wars, one realizes the complexity of life and the importance of following one own conscience. This was instrumental in my unconventional approach to life and science, which is far from accepting rules. I became convinced that reasoning and science are essential in an overwhelming world where speed and superficiality dominate, leaving insufficient time for deep thinking and creating a need for mental boundaries against information overload that otherwise fragments attention, diminishes discernment, and inhibits creative thought.

#### Please share with us what initially piqued your interest in your preferred area of research or professional focus.

Directing an important scientific center on top of maternity, surrounded by women before, during, and after giving birth, impacts your program,





University (Montreal, Canada), working with the late Krešimir Krnjević<sup>1</sup>, who was my only mentor, and with whom we discovered the failure of GABAergic inhibition in epilepsies. Returning to France, my keen interest was understanding how the amygdala operates, notably in seizure generation. During that period, I developed the kainic acid model of epilepsies and made seminal observations on how temporal lobe epilepsies are generated, showing how "seizures beget seizures" by a sequence of events including activity-dependent cell loss, and the formation of novel aberrant synaptic connections that will facilitate the generation of further seizures. My description paper of temporal lobe epilepsies (1985; DOI: 10.1016/0306-4522(85)90299-4) is amongst the most quoted papers on epilepsies.

In 1986, I was nominated head of an important INSERM unit located in a major maternity hospital (Port-Royal) and switched my interest from epilepsies to brain development. With my colleagues- notably Dr Enrico Cherubini, we discovered the GABA Excitatory /inhibitory developmental shift that has since then been observed in all animal species indicating that this is an evolutionary conserved rule. This shift, where GABA excites immature neurons before shifting to inhibition, is a fundamental process in brain development (for a review see DOI: 10.1038/nrn920). We also discovered a unique pattern of developing networks (GDPs) that are observed in various brain regions and animal species, including non-human primates in utero. More recently, I reported that parturition and birth are associated with a transient oxytocin-mediated GABAergic inhibition that exerts a neuroprotective and analgesic action during birth. Collectively, these observations illustrate vividly why the developing brain is not a small adult brain but one with unique features. The GABA shift is the best documented and investigated illustration of that.

In 2000, I moved with all my lab to the south of France and founded and directed a large institute (INMED) dedicated to brain development and disorders. An important observation made then was that in epilepsies and other disorders (notably autism), GABA again excites neurons - a 'return to an immature state.' This leads to the concept of Neuroarcheology (2008; DOI: 10.1016/j.tins.2008.09.002), in which I suggest that disorders born in utero are associated with misplaced / misconnected neuronal networks endowed with immature features that directly cause disorders- a sort of return to immaturity. Neuroarcheology challenges the notion of a direct link between the 'inaugurating insult' in utero and the disorder as the consequences of this event rather than the event itself being the target of treatments. Neuroarcheology proposes that many neurological disorders reactivate developmental mechanisms, providing a unifying framework connecting diverse scientific pursuits from basic research to clinical applications. Since then, we and several other labs have observed this concept in multiple brain disorders, suggesting a shared conceptual pathway. This had major fundamental and clinical implications that led to my next move upon retirement.

I decided to use my understanding of brain development and directly test the therapeutic implications of the Neuroarcheology concept using the NKCC1 inhibitor bumetanide shown by many groups and us to reduce (Cl<sup>-</sup>) I and restore the inhibitory drive. We showed that in several developmental disorders, notably autism, GABA excites neurons. Then, in two double-blind, andomized phase 2 trials, we showed that bumetanide

attenuates core symptoms of ASD in children. This finding was validated by seven other teams around the world (with over 1030 children treated successfully). However, despite that, our phase 3 failed, like, in fact, all phase 3 trials of developmental disorders (cf. Fragile X). I reasoned that this must be due to the heterogeneity of ASD and that a single treatment is unlikely to treat all forms of ASD. I therefore recruited AI experts, and we reanalyzed the phase 3 trial to find that, indeed, a significant % of children do respond to bumetanide and that specific clinical parameters can identify them. This paves the way for the identification of subpopulations of children with ASD that will be treated with bumetanide.

Then, I reasoned that ASDs are most likely born in the womb, suggesting that analysis of maternity data should enable the identification of babies who will be diagnosed with ASD later at birth. Using machine learning again, we showed that, indeed, at birth, almost all neurotypical children and almost half of those who will be diagnosed with ASD later can be identified. This directly demonstrates that ASD is born in utero and will facilitate an early use of psycho-educative tools to attenuate ASD.

Finally, as NKCC1 has been shown to be enhanced in brain tumors, I tested its actions preclinically on freshly removed brain tumors. It turned out that tumor cells need to reduce their volume and expulse water and ions to migrate, but another condition is required to kill cancer cells. I combined bumetanide with mebendazole, an agent known to destroy the cytoskeleton, and found that this combo both blocks migration AND kills most of the tumor cells in meningiomas, gliomas, and glioblastoma. My colleague, neuro-oncologist François Berger, and I tested the effects of the combo in a compassionate trial and found that this increased OS by > 9 months in a patient with an inoperable brain stem large metastasis. In parallel, we have now synthesized over 120 novel proprietary NKCC1 antagonists, some even more potent than bumetanide, that might be useful to treat many disorders.

Collectively, these studies illustrate the importance of developmental processes in disorders, both to predict them early and to treat them using the neuro archeology concept.

# What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

When facing a major unexpected observation, we tend to hesitate and consider this as being either unimportant or artefactual. It is much easier and safer to have precedents that are partly similar to those of other studies. Our discovery of the GABA actions shift was one that we left aside for over one year and failed to comprehend its major importance for two decades fully. Working on an evolutionary conserved rule is a stimulating, challenging, and massive endeavor. I will then spend the rest of my active life trying to understand its underlying mechanisms and implications fully. With more self-confidence, I should have rapidly realized that this domain is worth investing in.

#### What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you have maintained throughout your life?

My central value is to follow my intuition, although this is not a proper scientific approach. Scientists are not immune from their own "feelings," and one must accept the impact of one's education and environment on scientific observations (see the books of Stephen Jay Gould). In keeping with Jewish "Pilpul" (Hebrew: פָּלְפּוּל), which involves examining issues from multiple perspectives and defending both thesis and antithesis, I frequently advocate for different interpretations of my results to determine which explanation is most likely correct.

# Please tell us more about your most relevant focal points – past or present – within your chosen field of science. What were the key impact areas of your research topics?

I can think of two: First, temporal lobe epilepsies with the demonstration of how seizures beget seizures by an activity-dependent cell loss followed by the formation of aberrant pathways that will contribute to seizure generation. Additionally, an important focus was the fundamental role of the GABA excitatory to inhibitory developmental shift and the reverse

<sup>&</sup>lt;sup>1</sup>Krešimir Krnjević (1927–2021) was a Canadian-British neurophysiologist of Croatian origin. He stands as one of the most influential neuroscientists of the 20<sup>th</sup> century. His pioneering work revealed a groundbreaking discovery: aminoacids function as chemical messengers throughout the entire nervous system. Specifically, he identified gamma-aminobutyric acid (GABA) and glutamate as the primary inhibitory and excitatory signaling molecules in the brain, respectively. These discoveries revolutionized our understanding of how the nervous system operates. This fundamental work underpins modern neuropharmacology, particularly in the development of treatments for conditions like epilepsy, anxiety disorders, and neurodegenerative diseases. Krnjević's contributions earned him prestigious recognitions including the Gairdner International Award and appointment as Officer of the Order of Canada, cementing his legacy as a pioneering figure whose research continues to inform neuroscience today. His extraordinary autobiography is freely available at this link. http://www.amcaqc.org/Common/Docs/Files/6037/kk\_sfn.pdf





**Figure 2.** The ancient olive tree (estimated > 250 years old) in Yehezkel Ben-Ari's Mediterranean garden showcases climbing roses intertwining with its gnarled trunk and branches. This botanical integration exemplifies Ben-Ari's interest in cultivating rare plants and his appreciation for natural environments, which he describes in the interview as providing moments of respite and inspiration for his scientific work. The garden setting near the sea reflects his preference for locations that foster both contemplation and innovation.

situation in brain disorders. The Neuroarcheology concept will remain a major lead to understanding and treating many brain disorders.

# What have you most enjoyed in your capacity as an academic or research leader?

In the academic sphere, I have enjoyed establishing and guiding a substantial institute with distinctive characteristics that integrate fundamental and practical scientific approaches in one setting, alongside art collection displays and a hands-on learning school. This school welcomes high school students, primarily from disadvantaged communities, to experience the wonder of scientific experimentation and reasoning through direct participation.

Personally, I have found deep satisfaction in creating startups focused on treating autism and brain tumors based on unconventional insights derived from straightforward biophysical principles. It brings me immense joy to receive gratitude from parents whose children with ASD have progressed to high school thanks to our bumetanide treatment approach.

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 you feel strongly devoted to?

Yes, I believe that discoveries are always made on side roads, never on highways, implying that it is crucial to migrate from one domain to an-

other rather than do all your life the same thing and become the world expert on neuron X or molecule Y. This latter approach facilitates life, enabling good observations and excellent publications but does not result in genuine discoveries. Nowadays, scientists do not have the time to think, as they devote too much effort to writing grants. An astrophysicist friend and colleague (A. Brahic, now deceased<sup>2</sup>) used to say that half our scientists spend their lives writing grants, while the other half will spend their lives evaluating them. I am convinced that giving large grants to scientists who have shown excellence in one domain, provided they change the domain, would be an excellent way to efficiently finance scientific research.

#### 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 live close to the sea in a large estate where I cultivate rare fruits, vegetables, and flowers; gardening and bird watching are excellent ways to detach from science, freeing one's mind from ongoing problems and leading to innovative ideas.

# Part 2: Yehezkel Ben-Ari – Selected questions from the Proust Questionnaire<sup>3</sup>

What is your most marked characteristic? Breaking from convention.

Among your talents, which one(s) give(s) you a competitive edge? Breaking from convention.

If you could change one thing about yourself, what would it be? To have more patience.

#### What is your current state of mind?

Optimistic for my line of research and treatment but pessimistic about the future.

#### What is your idea of perfect happiness?

As Sartre suggested, life consists of brief moments of joy interspersed among complications. Finding these fleeting instances of happiness amid life's challenges is perhaps as close to perfection as we can hope for.

When and where were you happiest? And why were you so happy then? Personally: The day of my marriage—a moment of profound connection and commitment.

Professionally: Two moments stand out—first, when I inaugurated INMED with a remarkable series featuring exceptional musicians from

<sup>2</sup>French astrophysicist André Brahic died in Paris on 15 May 2016 at the age of 73 after a battle with cancer. An expert on the solar system, in 1984, he launched a program that led to the discovery, with US astronomer William Hubbard, of the rings around the gaseous planet Neptune. In 1990, an asteroid, number 3488, was named in his honor. He was awarded the Carl-Sagan 2000 prize, the Jean-Perrin 2006 prize for popularising scientific knowledge, and the Légion d'Honneur (2015).

<sup>3</sup>In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35question 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.



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across Mediterranean countries, and second, when I succeeded in bringing together Israeli and Arab neuroscientists for a groundbreaking scientific exchange.

#### What is your greatest fear?

Where the world is going.

#### What is your greatest regret?

Not always being able to recognize important observations.

#### What are you most proud of?

Being able to shift from very basic science to developing treatments and even reaching the phase 3 trial stage (autism); these are very different domains that require very different capacities.

What do you consider your greatest achievement? In science: discovering the GABA developmental shift.

What or who is your greatest passion?

Writing on science and other aspects of life.

#### What is your favorite occupation (or activity)?

Listening to Jascha Heifetz and classical music, notably Alfred Deller or Rubenstein.

### What is your greatest extravagance?

I am afraid that this is not in my temperament.

### What is your most treasured possession?

A collection of sculptures and paintings.

#### Where would you most like to live?

Where I do live not far from the sea.

#### What is the quality you most admire in people? Capacity to find links between domains that are not obviously linked.

#### What is the trait you most dislike in people? Excessive pride.

What do you consider the most overrated virtue? Intelligence.

What do you most value in your friends? Open-mindedness.

Which living person do you most admire? I prefer not to make such distinctions.

#### Who are your heroes in real life?

I find heroism in different people for different reasons; it is impossible to name just a few.

# If you could have dinner with any historical figure, who would it be and why?

Either Mozart or Champollion. I am fascinated by what true genius actually means and how it manifests in different fields, whether in musical composition or deciphering ancient languages.

#### Who are your favorite writers?

Stephen Jay Gould, Chris Hedges, David Graeber, Russian writers (Dostoyevsky, Gogol), and of course Hugo and Balzac.

#### Who are your heroes of fiction?

I am not someone who idolizes imaginary heroes.

#### What aphorism or motto best encapsulates your life philosophy? Be moved by music and lack of justice.

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#### Yehezkel Ben-Ari<sup>1</sup> 🝺

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