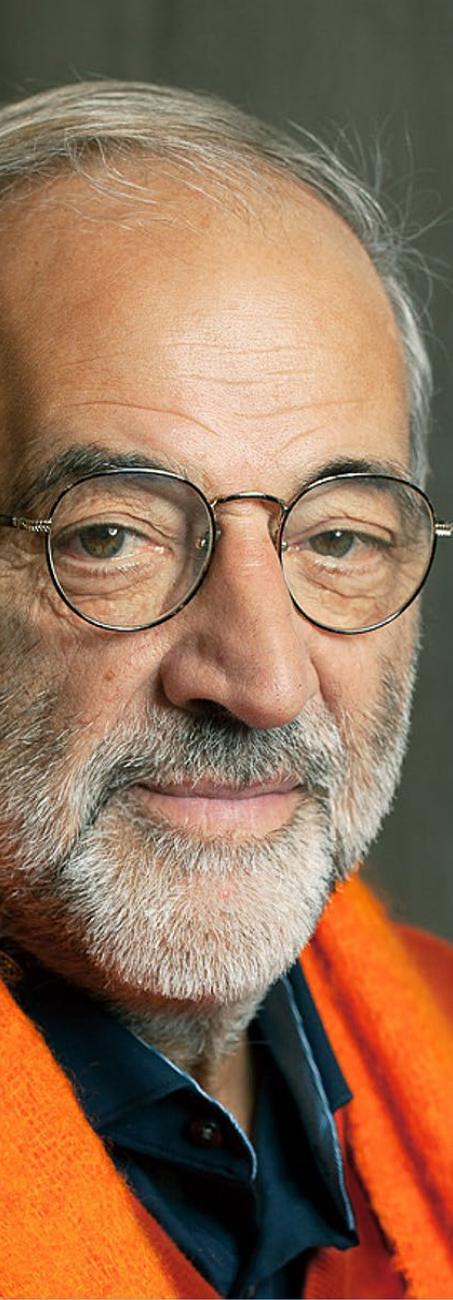


NKCC1 & MICROTUBULE INHIBITORS TO TREAT BRAIN TUMORS





Yehezkel Ben-Ari, a founder serving innovation

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5 DECADES OF ACADEMIC & PRIVATE RESEARCH

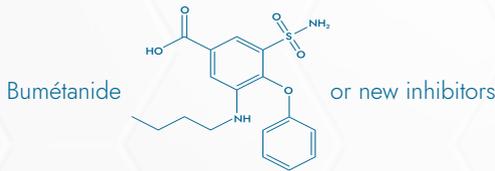
- > 4 decades academic research on brain development and disorders, major discoveries on electrical signatures of brain development and pathology
- > More than 520 publications, amongst the most quoted 5 French neuroscientists & important awards including the French National Institute of biomedical research (INSERM) grand prix, the European and US epilepsy foundations, the Belgian Gagna Van Haeck & Doct. Hon. Causa of Liege University
- > 15 years private Founder & CEO of Neurochlore & BA-oncomedical -dedicated to treat autism and brain tumors



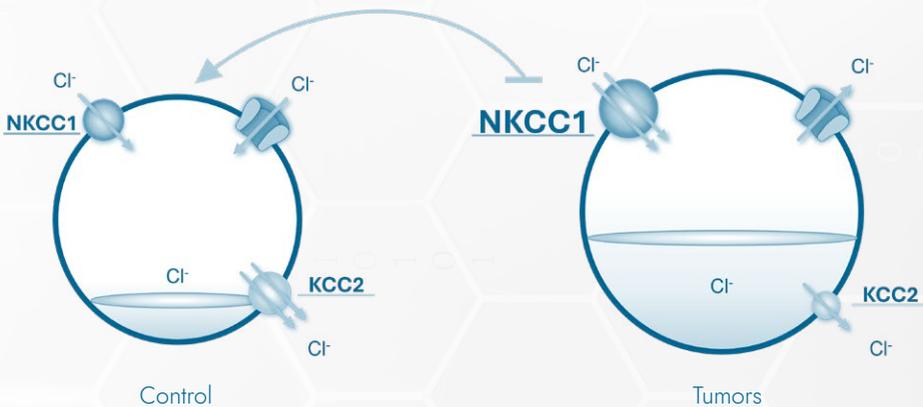
- > en.wikipedia.org/wiki/Yehezkel_Ben-Ari
- > linkedin.com/in/yehezkel-ben-ari
- > leblogdebenari.com/en
- > ben-ari.fr



THE NKCC1 CO-TRANSPORTER IS INSTRUMENTAL IN BRAIN TUMORS



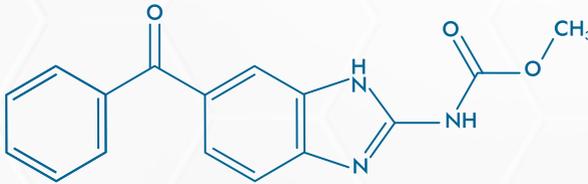
NKCC1 inhibition



- NKCC1 controls $(Cl^-)_i$ levels & cell volume & its activity is increased in brain tumors
- NKCC1 is present on the leading edge of the metastatic protrusion
- Bumetanide attenuates the severity of tumors in animal models, human cell lines and brain tumoroids
- Adding Bumetanide to Temozolomide increases its anti-cancer activity
- The activity of NKCC1 correlates with the grade severity of Glioblastoma in patients

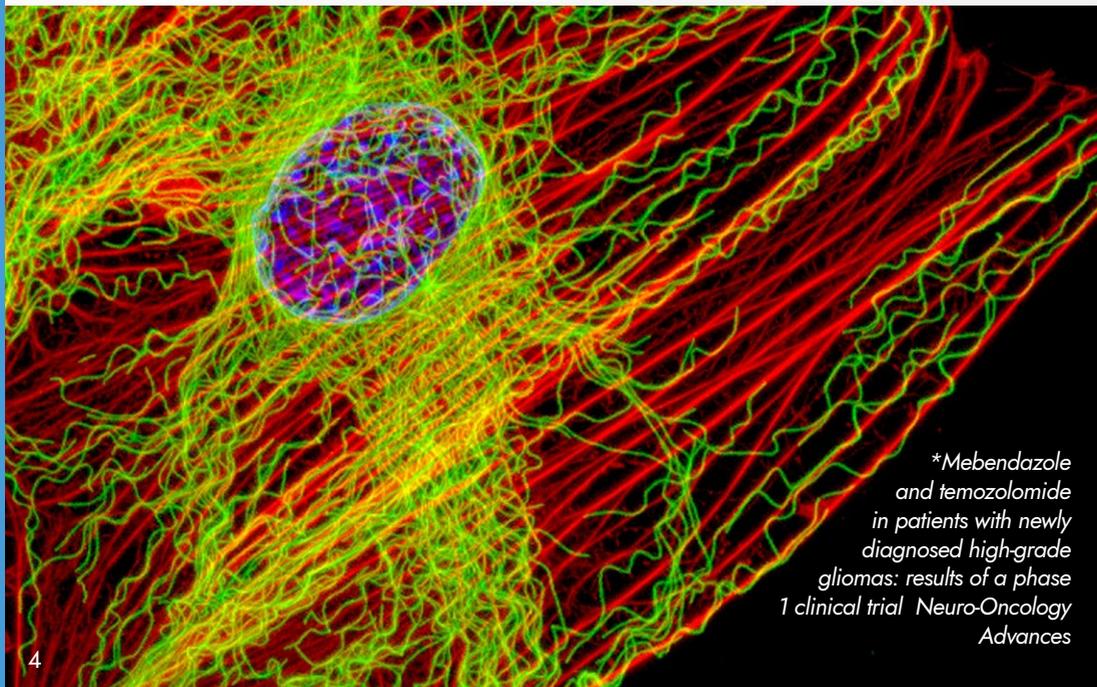
MICROTUBULE INHIBITORS ARE INSTRUMENTAL IN BRAIN TUMORS

➤ In experimental conditions, anthelmintic drugs like Mebendazole augment apoptosis and attenuate tumors



Mebendazole

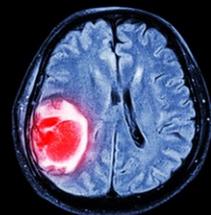
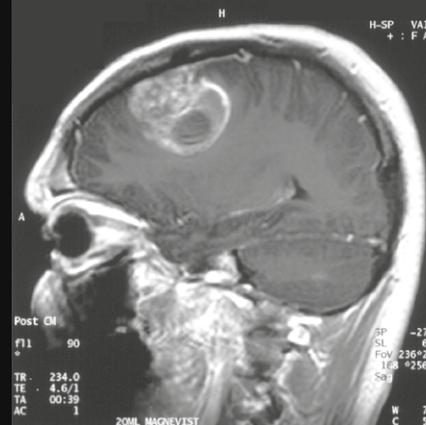
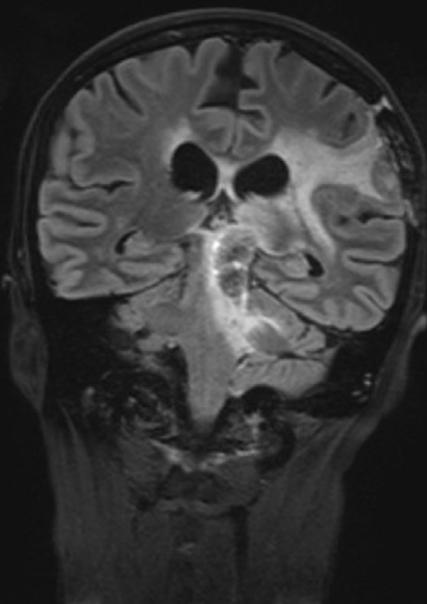
➤ Mebendazole administered with Temozolomide demonstrated a 21-month survival time at 2 years (*Kaplan-Meier analysis*) & long terms safety, acceptable toxicity (*Gallia et al 2021*)*



*Mebendazole and temozolomide in patients with newly diagnosed high-grade gliomas: results of a phase 1 clinical trial Neuro-Oncology Advances

COMPLEMENTARY ACTIONS OF MEBENDAZOLE & BUMETANIDE TO TREAT BRAIN TUMORS

- Since the targets & mechanisms of action of both drugs differ, we tested the effects of combining their applications
- In rodent cortical slices, incubation with Mebendazole strongly enhances bumetanide efficacy to block seizures
- In Brain tumoroids, combined applications of Mebendazole and Bumetanide have more powerful effects than either alone
- In a pilot compassionate trial, administration of the combo enhanced survival significantly without additional side effects

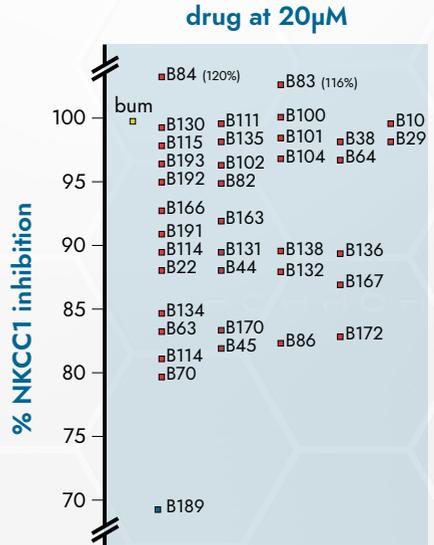


SECOND GENERATION PROPRIETARY NKCC1 INHIBITORS TO TREAT BRAIN TUMORS

> We have synthesized, and **patent protected** 120 novel NKCC1 inhibitors, some are as or even more efficient than Bumetanide to lock NKCC1

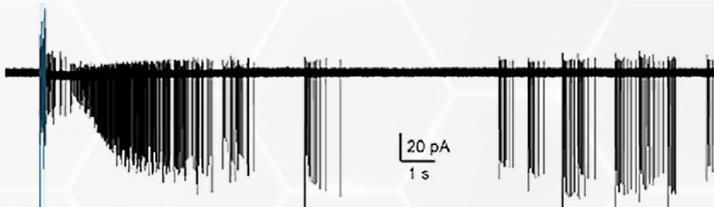
> In Human cell lines and freshly resected tumoroids, many molecules enhance apoptosis and attenuate migration at μM dosages

> In rodent Hippocampal slices, many molecules reinforce GABAergic inhibition with an antiepileptic activity



Control P15
(3 consecutive traces superimposed)

Cell-attached recordings
Tetanus (20 stimulus, 100Hz)



B50 2 μM (3 consecutive traces superimposed)

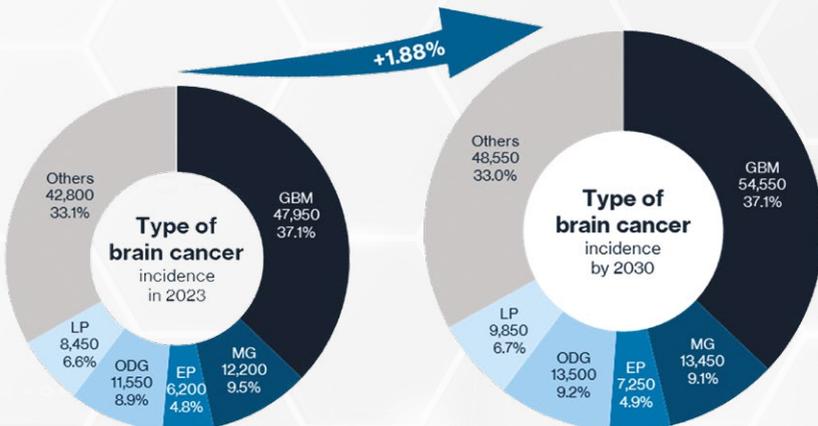
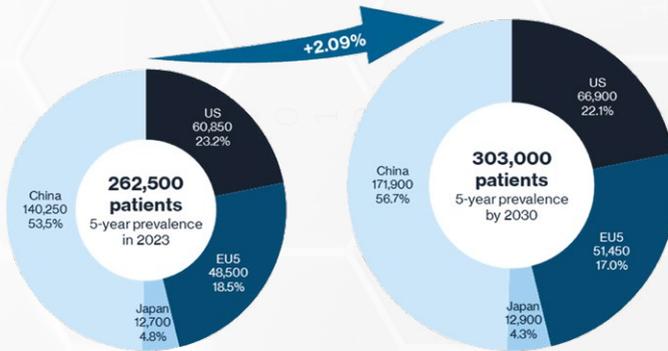
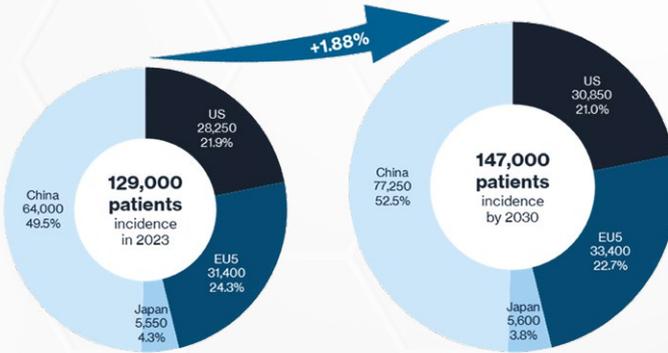


OUR AIMS: A DUAL STRATEGY TO TREAT BRAIN TUMORS

- › Phase 2/3 clinical trials with Bumetanide & Mebendazole
- › Selecting the best Novel NKCC1 Inhibitors to IND-enabling studies and phase 1
- › We have a collection of proprietary powerful NKCC1 inhibitors
- › Large body of evidence suggests that NKCC1 inhibitors are putative treatments for many other disorders including brain trauma, epilepsies, CVI, Alzheimer disease, chronic pain, autism & developmental disorders, various cancers etc

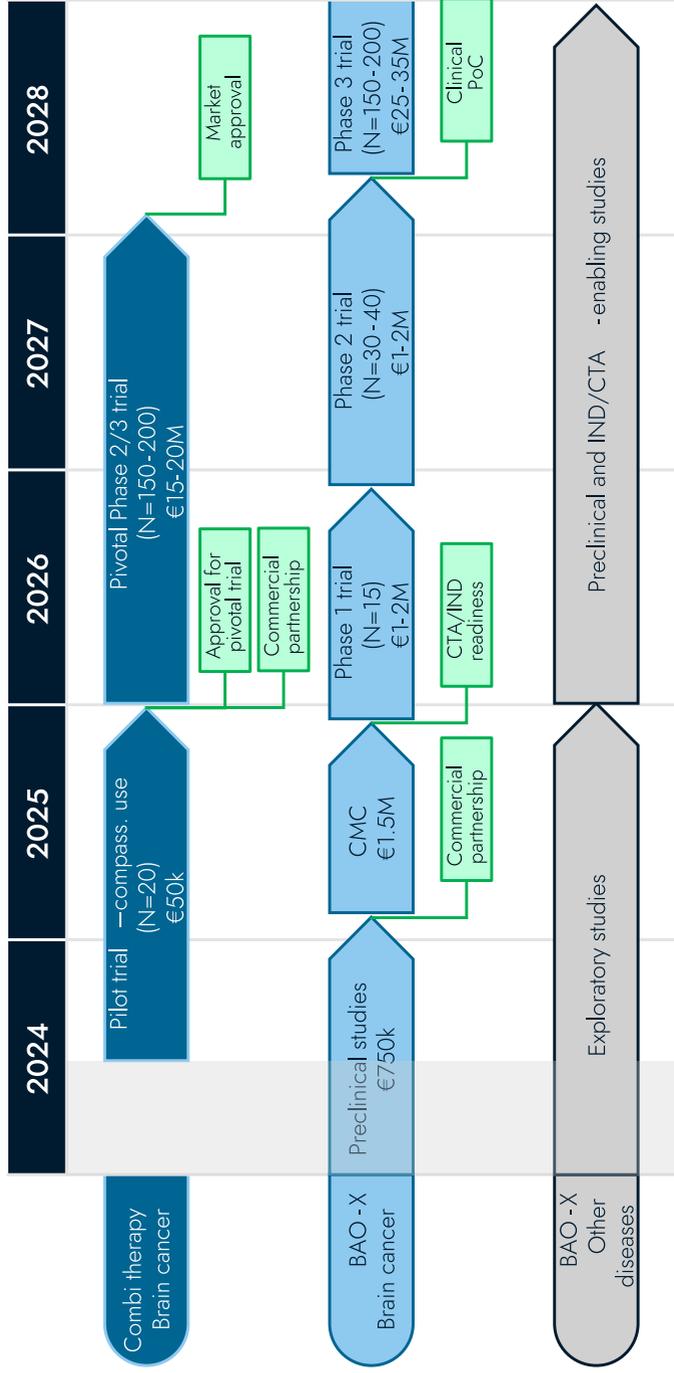


STRIVING TO TACKLE THE UNMET NEEDS TO TREAT BRAIN TUMORS



GBM:Glioblastoma | MG:Meningioma | EP:Ependymoma | ODG:Oligodendroglioma | LP:CNS Lymphoma

A DUAL STRATEGY FOR CAPTURING THE MARKET



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