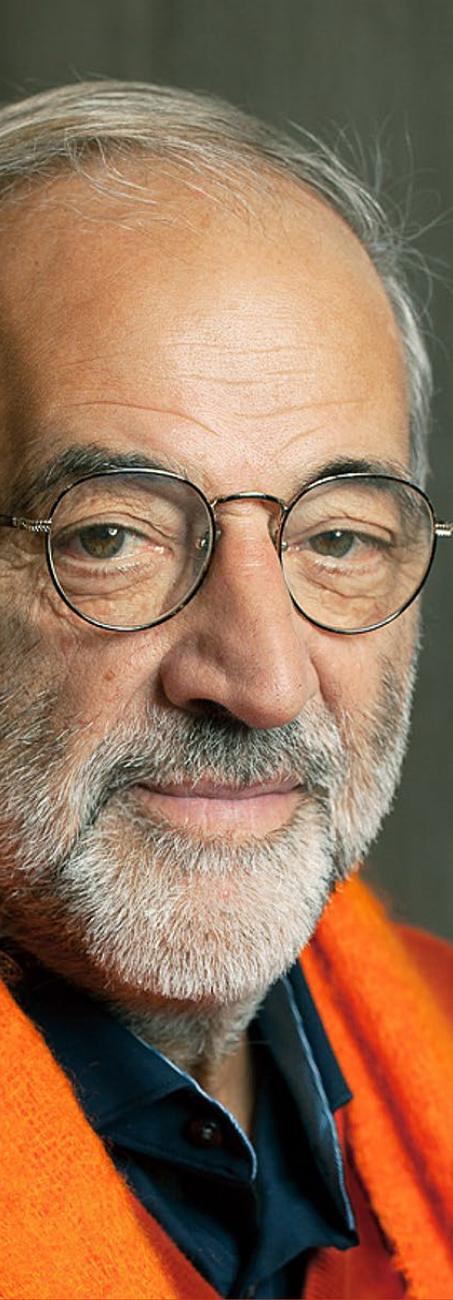


NKCC1 INHIBITORS  
TO TREAT AUTISM :  
**NEW VISTAS**



**NEUROCHLORE**





# Yehezkel Ben-Ari, a founder serving innovation

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## 5 DECADES OF ACADEMIC & PRIVATE RESEARCH

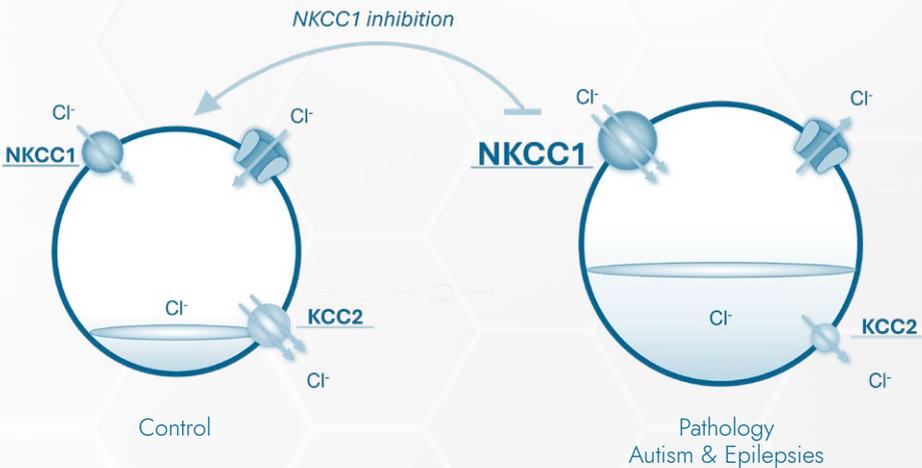
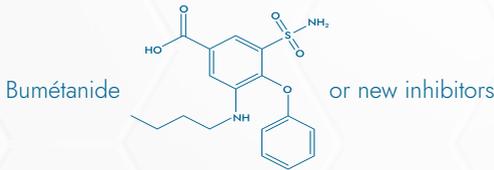
- > 4 decades academic research on brain development and disorders, major discoveries on electrical signatures of brain development and pathology
- > More than 520 publications, amongst the most quoted 5 French neuroscientists & important awards including the French National Institute of biomedical research (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](https://en.wikipedia.org/wiki/Yehezkel_Ben-Ari)
- > [linkedin.com/in/yehezkel-ben-ari](https://linkedin.com/in/yehezkel-ben-ari)
- > [leblogdebenari.com/en](https://leblogdebenari.com/en)
- > [ben-ari.fr](https://ben-ari.fr)



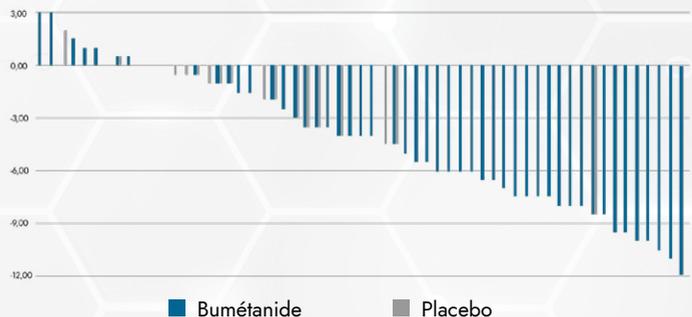
# NKCC1 INHIBITORS ATTENUATE MANY BRAIN DISORDERS



- > The equilibrium between NKCC1 (importer) & KCC2 (exporter) regulates GABAergic inhibition & cell volume.
- > NKCC1 activity is increased -and KCC2 activity decreased- in Autism, epilepsies, Fragile X, brain trauma, Huntington disease, etc (*Ben-Ari TINS 2021*).
- > Inhibiting NKCC1 (sans activity) restores GABAergic inhibition & attenuates many disorders including autism, fragile X, epilepsies etc. (*Savardi et al TIPS et al 2021, Ben-Ari TINS 2021*).

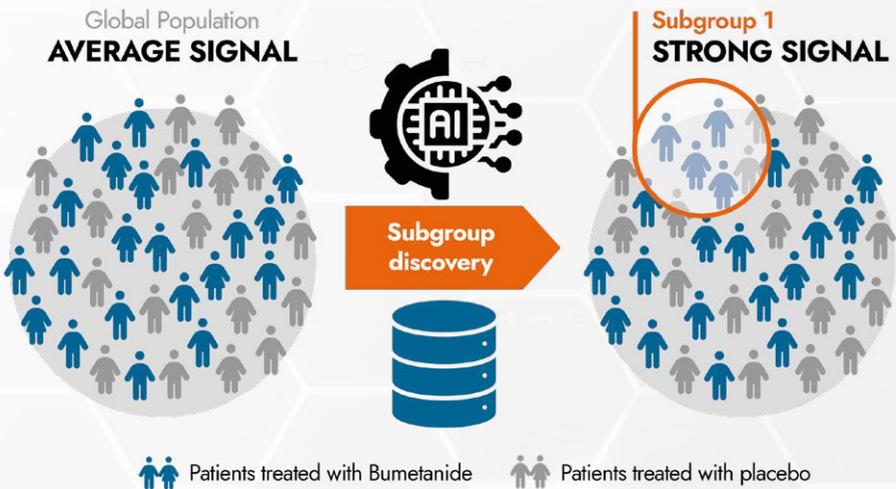
# BUMETANIDE ATTENUATES AUTISM IN CHILDREN AND ADOLESCENTS

- Bumetanide attenuates autism severity in our 2 trials & in 7 other phase 2 trials (>1030 children) performed in many different countries (*Xiao et al 2024*)
- Bumetanide ameliorates visual interactions, identification of emotive figures and functional MRI alterations (*Hadjikhani et al 2018*)
- A phase 3 trial using as a principal criterion CARS2 - a sum of 15 different items- failed because it did not consider the heterogeneity of autism (*Fuentes et al 2023*)
- Bumetanide responders can be predicted from EEG (*Juarez-Martinez et al 2021*) or immunological parameters (*Li et al 2021*) suggesting different biological features of responders and non-responders



# IDENTIFYING SUBPOPULATIONS OF BUMETANIDE RESPONDERS

- To identify bumetanide responders, we used Machine Learning to analyze all the rating subscales included in phase3:SRS (65 items), CARS (15 Items) & DSM (4 items)
- We succeeded to identify 30% to 40% responder subgroups relying on dual combinations of rating subscales (*Rabiei et al in prep*)
- A phase 3 relying on these inclusion criteria is most likely to succeed

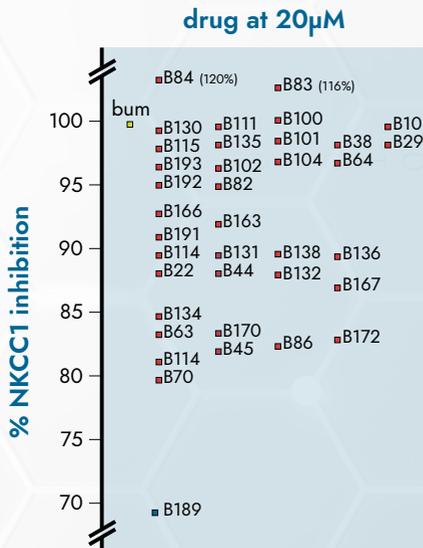


## PATENT:

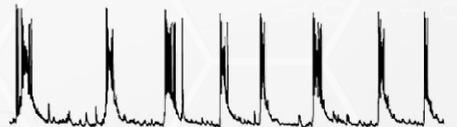
«Treating with Bumetanide clinically identified children & adolescents with autism»

# NOVEL NKCC1 INHIBITORS TO TREAT AUTISM

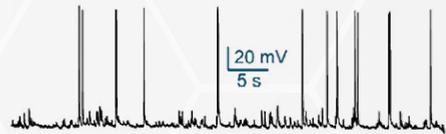
- > We have synthesized 120 novel NKCC1 inhibitors some with 75 to 120% bumetanide efficacy on ion efflux
- > Our novel inhibitors reinforce GABAergic inhibition & block seizures in rodent hippocampal brain slices



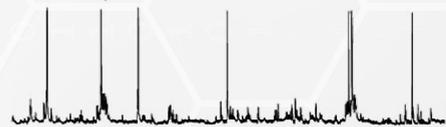
Control, P5-7m, 4-AP (100  $\mu$ M) incubation 2h



B111 10  $\mu$ M



B135 10  $\mu$ M



## PATENT:

«Novel NKCC1 inhibitors to treat autism, epilepsies, and many other disorders»

# OUR AIMS: A DUAL APPROACH TO TREAT AUTISM

- Phase 2/3 clinical trials: Validating identified subgroups of children responsive to Bumetanide for autism treatment
- Marketing bumetanide to treat a subpopulation of clinically identified children with autism
- Selecting the best candidates of Novel NKCC1 Inhibitors to IND-enabling studies and phase 1
- The largest collection of tested & protected NKCC1 inhibitors analogs to treat autism and many other disorders



# STRIVING TO TACKLE THE UNMET NEEDS IN AUTISM SPECTRUM DISORDER

## A complex disorder with symptoms that vary from person to person

- Routine, Repetitive and restrictive behaviour
- Extreme anxiety
- Focussed interests and memory
- Social Communication and Interaction Challenges
- Over-or-under sensitivity
- Meltdown / shutdown

Current standard of care necessitates a complex, individualised approach to deal with the heterogeneity of ASD, with no curative treatment available.

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## A global challenge affecting over 28M people



Approximately **1/100** children are diagnosed with ASD around the world. Prevalence is higher in the US, with **1 in 36** 8 year old likely to have ASD.



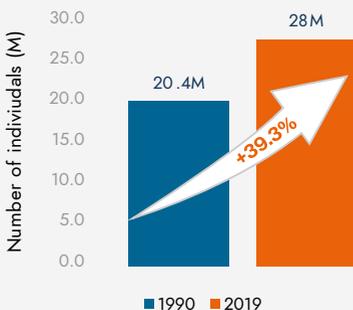
ASD appears to be **more prevalent in males** than females in a **ratio of 3:1**.



**Direct and indirect costs of caring** for ASD suffers in the United States are estimated at over **\$270 billion**.

The cost of **education, health care, and other lifelong services** for an autistic patient varies from **\$1.4 million to \$2.4 million per year**.

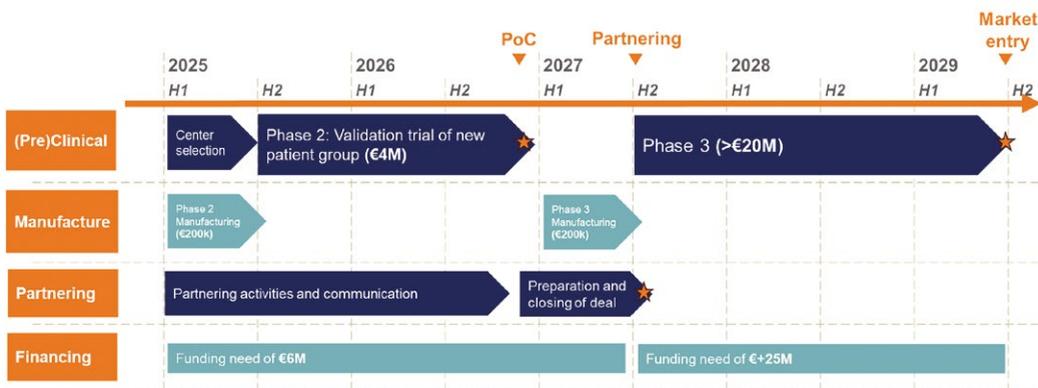
Global ASD Prevalence 1990 - 2019



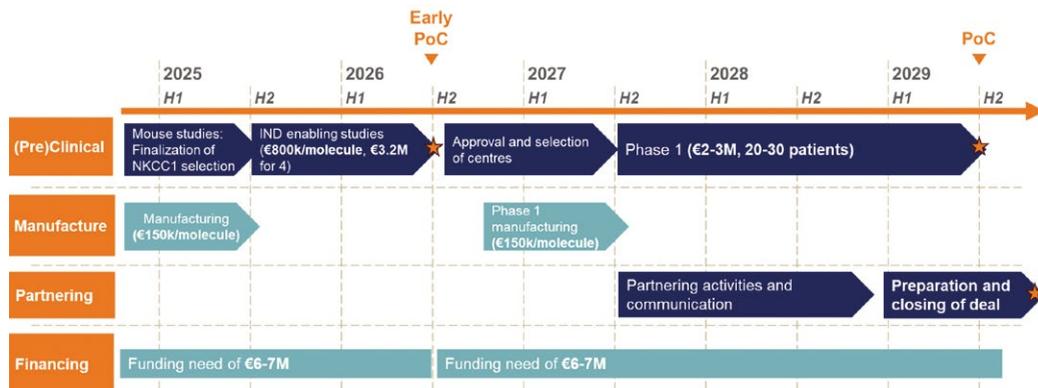
We have the opportunity to break into a therapeutic market valued at over **\$34B**, offering a first class solution to **treat the core symptoms of ASD**

# A DUAL STRATEGY FOR CAPTURING THE MARKET

## BUMETANIDE Critical steps to market



## NEW NKCC1 INHIBITORS Critical steps to market



# CONTACT



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