News about the ADNP Syndrome

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Laboratory Members:

Ph.D. students: Yanina Ivashco-Pachima, Adva Hadar, Iris Grigg, Gal Hacohen-Kleiman, Oxana Kapitansky, Shlomo Sragovich and Gideon Karmon (MD/PhD student). Master Students: Yael Toren, Nofar Herman and Aman Gaaim. Dr. Eliezer Giladi, Ph.D., Laboratory Manager. Professor Joseph Levine, Sabbatical.

משרד המדע, הטכנולוגיה והחלל

מדינת ישראל
משרד הבריאות
Ministry of Health Israel

ERA-NET NEURON

ISRAEL SCIENCE FOUNDATION

AMN Foundation, Spanish & French Friends of Tel Aviv University, Drs. Ronith and Armand Stemmer, Mr Arthur Gerbi

BSF United States – Israel Binational Science Foundation

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Adams Super Center for Brain Studies
Tel Aviv University

Sagol School of NEUROSCIENCE Tel Aviv University

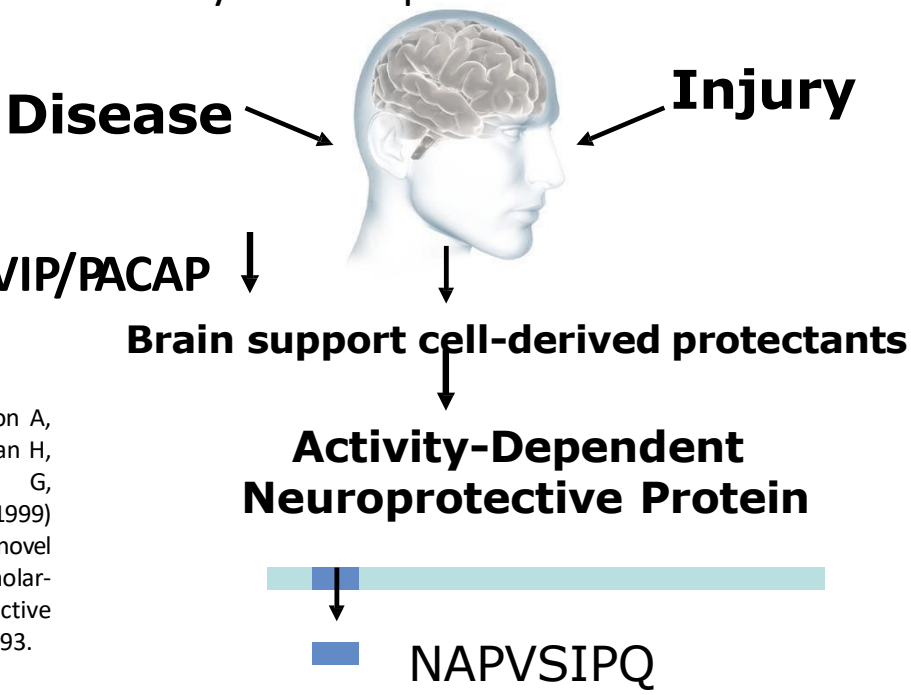
CORONIS NEUROSCIENCES

Professor Illana Gozes
Chief Scientific Officer

The Naomi Foundation
The Eldee Foundation/ Bloomfield Family of Montreal awards

Our Discovery: Activity-Dependent Neuroprotective Protein (ADNP)

Discovery of brain protective molecules



Bassan M, Zamostiano R, Davidson A, Pinhasov A, Giladi E, Perl O, Bassan H, Blat C, Gibney G, Glazner G, Brenneman DE, Gozes I (1999) Complete sequence of a novel protein containing a femtomolar-activity-dependent neuroprotective peptide. J Neurochem 72:1283-1293.

ADNP platform

- CP201 (*Davunetide*; NAP)
- **ADNP syndrome**
  - Alzheimer's disease and schizophrenia

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Our Discovery:
Activity-Dependent Neuroprotective Protein (ADNP)

ADNP is essential for brain formation and function: **No ADNP - No Brain**
In mice: half the content of ADNP results in **severe cognitive impairments**
ADNP mutations in children result in an autism spectrum disorder – **ADNP syndrome**

Normal Embryo

ADNP Knockout has disrupted brain formation: Dies in utero

Refs:
J Neurochem. 1999 Mar;72(3):1283-93.
J Biol Chem. 2001 Jan 5;276(1):708-14.
Brain Res Dev Brain Res. 2003 Aug 12;144(1):83-90.
J Pharmacol Exp Ther. 2007 Nov;323(2):438-49.
Mol Psychiatry. 2016 Oct;21(10):1467-76
Transl Psychiatry. 2015 Feb 3;5:e501.

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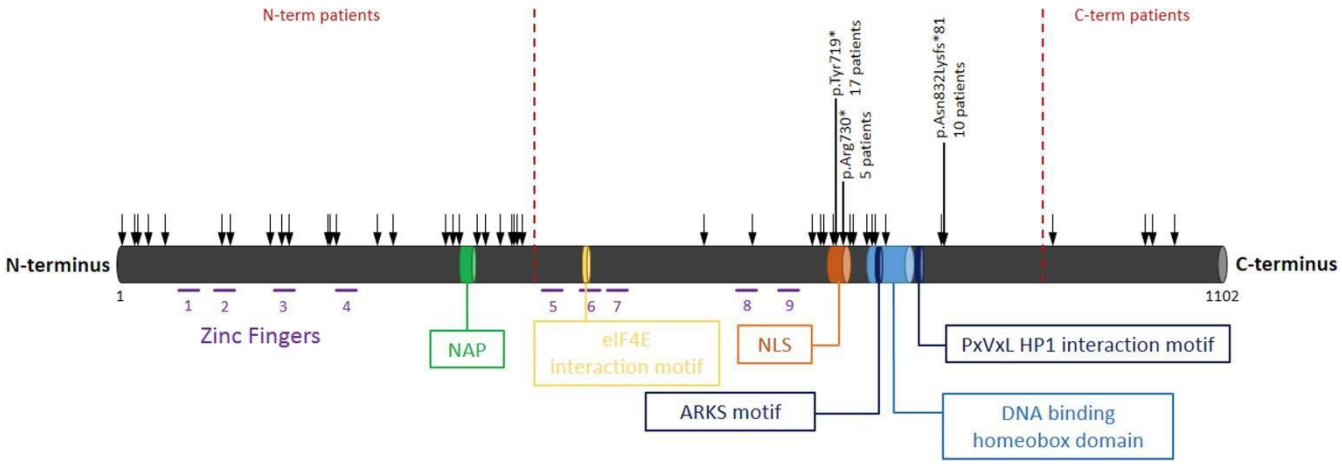
The ADNP Gene Mutations: The ADNP Syndrome Affecting Neurodevelopment



Refs:
J Neurochem 72:1283-1293.
J Biol Chem. 2001 Jan 5;276(1):708-14.
J Alzheimers Dis. 2015 Jan 1;45(1):57-73. doi: 10.3233/JAD-142490.

Van Dijck A, Vulto-van Silfhout AT, Cappuyns E, van der Werf IM, Mancini GM, Tzschach A, Bernier R, Gozes I, Eichler EE, Romano C, Lindstrand A, Nordgren A; ADNP Consortium, Kvarnung M, Kleefstra T, de Vries BBA, Küry S, Rosenfeld JA, Meuwissen ME, Vandeweyer G, Kooy RF.
Clinical Presentation of a Complex Neurodevelopmental Disorder Caused by Mutations in ADNP.
Biol Psychiatry. 2019 Feb 15;85(4):287-297. doi: 10.1016/j.biopsych.2018.02.1173.

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Indication: ADNP Syndrome

- ADNP is one of the most frequently mutated genes within the Autism Spectrum Disorder – 0.17% of the autistic patients
- 60% Males / 40% Females
- ADNP syndrome is caused by de novo stop mutations in the ADNP gene
- Symptoms manifest early and include abnormalities in a range of sensory, motor and cognitive functions: Intellectual disability, Cognitive disorders, Social deficits and Motor development delay
- ADNP Patients are detectable through premature primary tooth eruption

ADNP syndrome | Healthy Twin

ASD Prevalence[1]
~9000 ADNP Patients

ASD Prevalence[2]
~10000 ADNP Patients

Prevalence is estimated at approximately 1:35000 – 1:60000

[1] WHO estimate 1:100
[2] CDC Estimates 1:59 (2018)

Ref1:
Biological Psychiatry DOI: (10.1016/j.biopsych.2018.02.1173)
Ref2:
J Mol Neurosci. 2015 Aug;56(4):751-757
Translational Psychiatry (2017) 7, e1043
Front Endocrinol (Lausanne). 2017 May 19;8:107.

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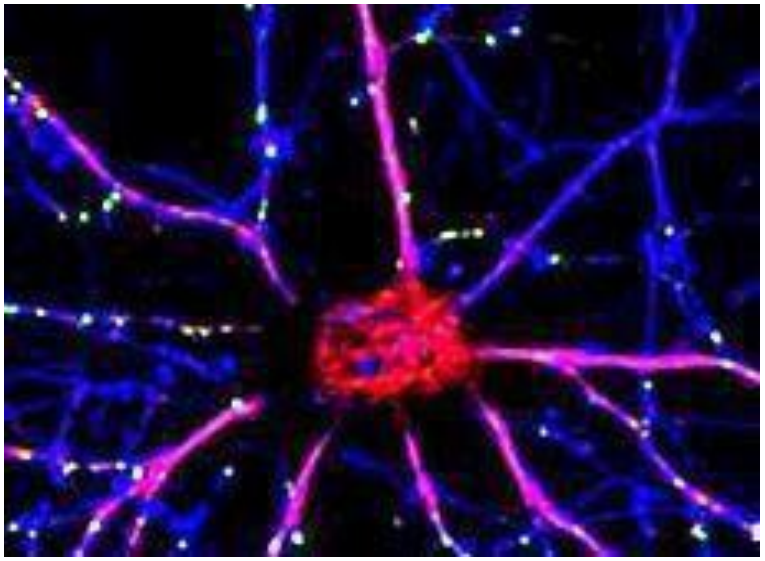
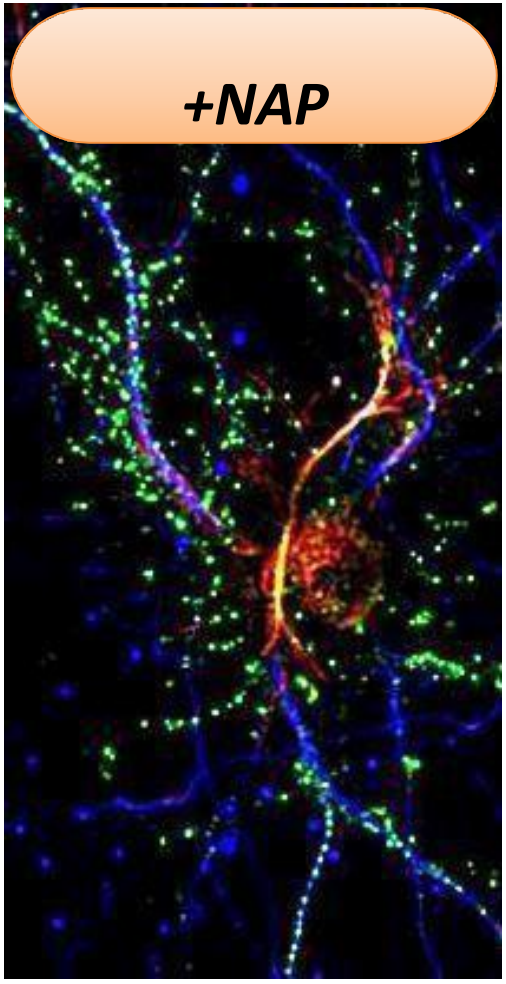
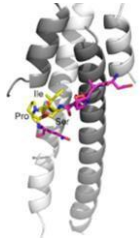
The NAP-Motif of Activity-Dependent Neuroprotective Protein (ADNP) Regulates Dendritic Spines through Microtubule End Binding (EB) Proteins



Synapse Formation

+NAP





Mol Psychiatry. 2016 Oct;21(10):1467-76.
Sci Rep. 2016 Nov 10;5:16300.

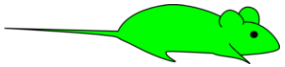
NAP/ADNP: increases synaptic connections through EB (green)

NAP enhances ADNP activity: Microtubule fortification

"Molecules that make our minds"

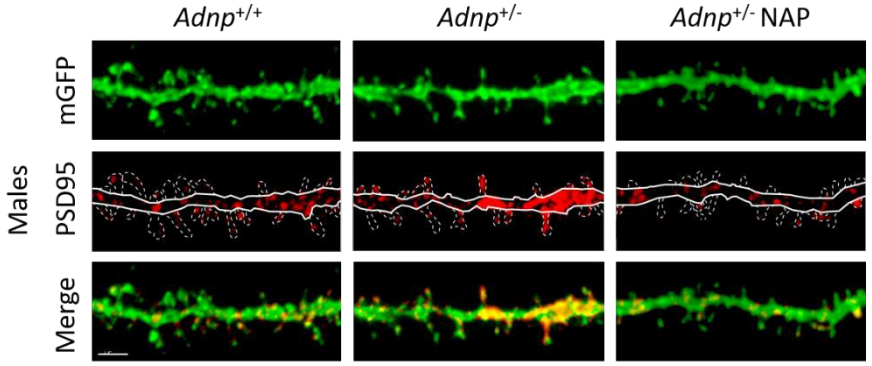
Oz S, Kapitansky O, Ivashco-Pachima Y, Malishkevich A, Giladi E, Skalka N, Rosin- Arbesfeld R, Mittelman L, Segev O, Gozes I.
The NAP-Motif of Activity-Dependent Neuroprotective Protein (ADNP) Regulates Dendritic Spines through Microtubule End Binding Proteins
Mol Psychiatry. 2014 Oct;19(10):1115-24.

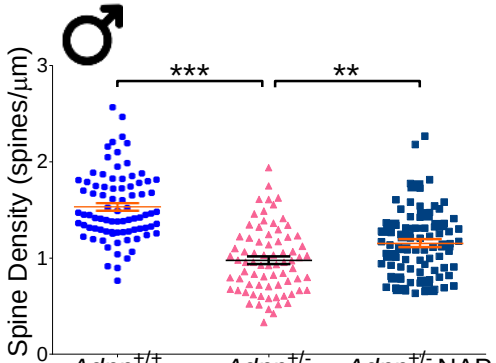
ADNP$^{+/-}$: Synapse Deficiency Reversed by NAP (CP201)

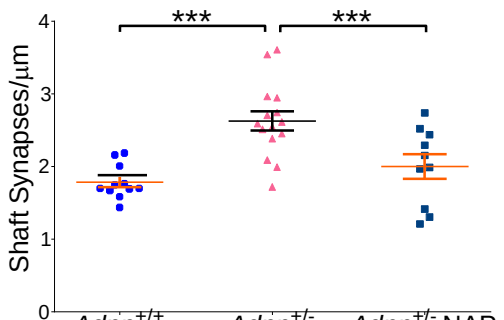


Hippocampus – learning and memory

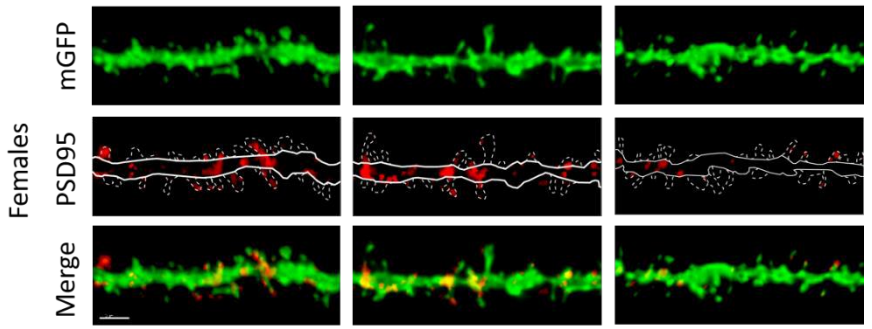
A)

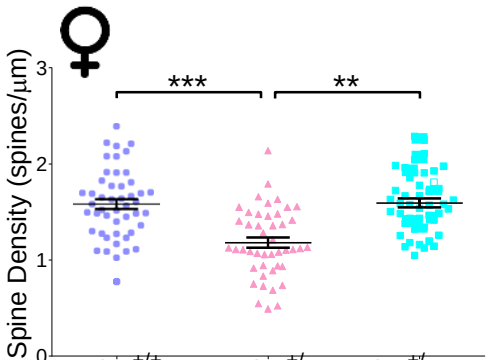


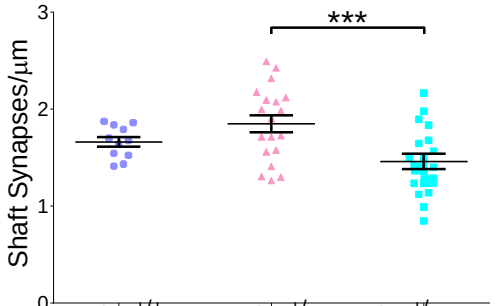




B)

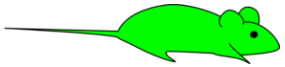






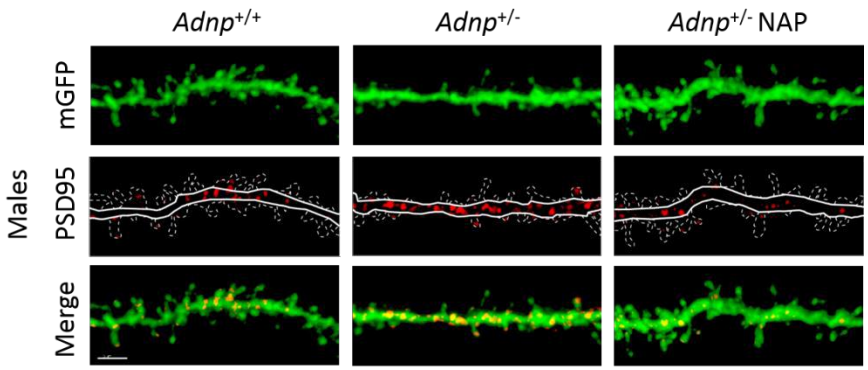
Activity-dependent neuroprotective protein deficiency models synaptic and developmental phenotypes of autism-like syndrome.
Hacohen-Kleiman G, Sragovich S, Karmon G, Gao AYL, Grigg I, Pasmanik-Chor M, Le A, Korenková V, McKinney RA, **Gozes I**. J Clin Invest. 2018 Nov 1;128(11):4956-4969

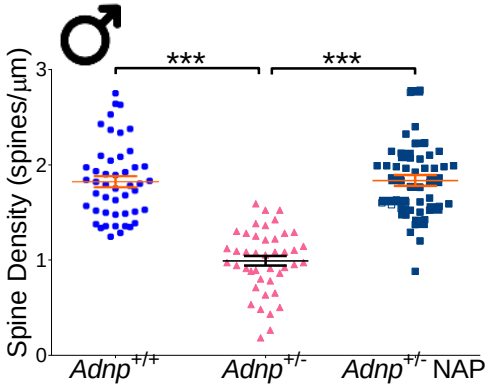
ADNP$^{+/-}$: Synapse Deficiency Reversed by NAP (CP201)

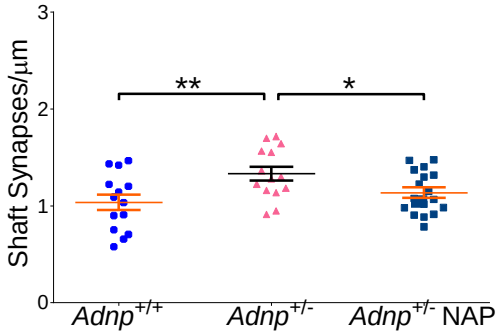


Cerebral cortex – motor function

A)



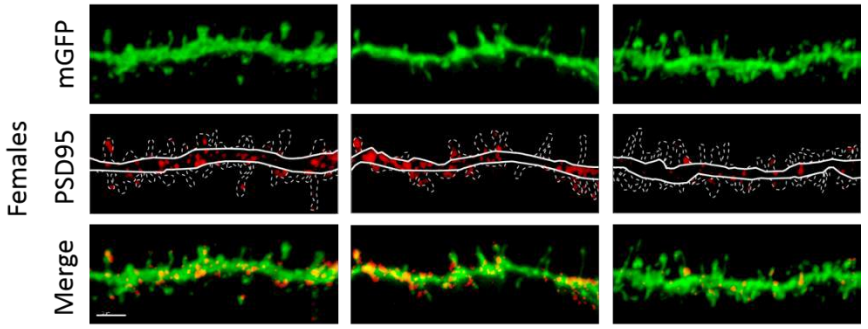


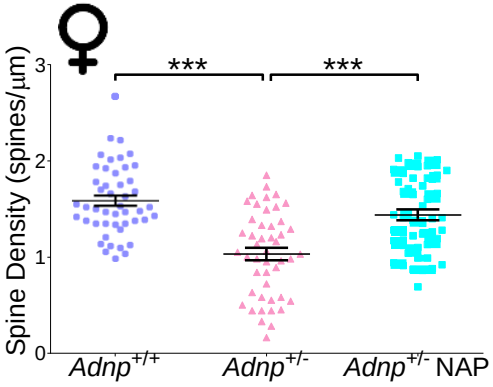


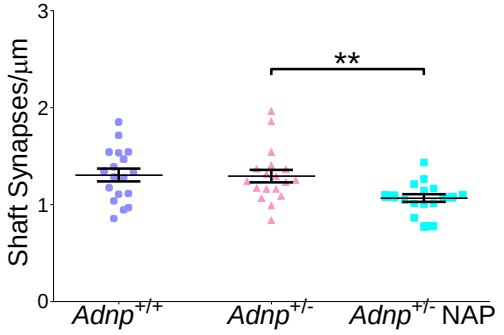
1.82±0.06 0.99±0.05 1.83±0.06

1.04±0.08 1.33±0.07 1.13±0.05

B)







1.59±0.05 1.03±0.06 1.44±0.05

1.30±0.06 1.29±0.07 1.07±0.04

Hacohen-Kleiman G, Sragovich S, Karmon G, Gao AYL, Grigg I, Pasmanik-Chor M, Le A, Korenková V, McKinney RA, **Gozes I**.
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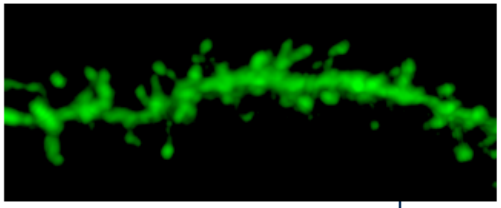
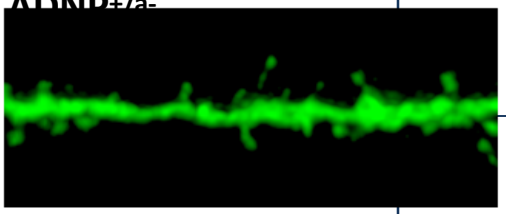
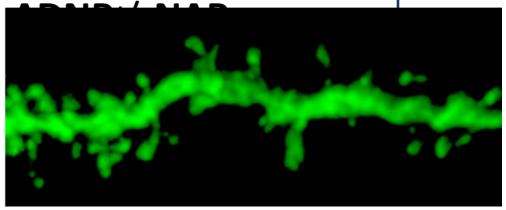
Drug Candidate **CP201 MoA** in vivo

ADNP-deficiency – synapse deficiency CP201 repairs

ADNP$^{+/+}$







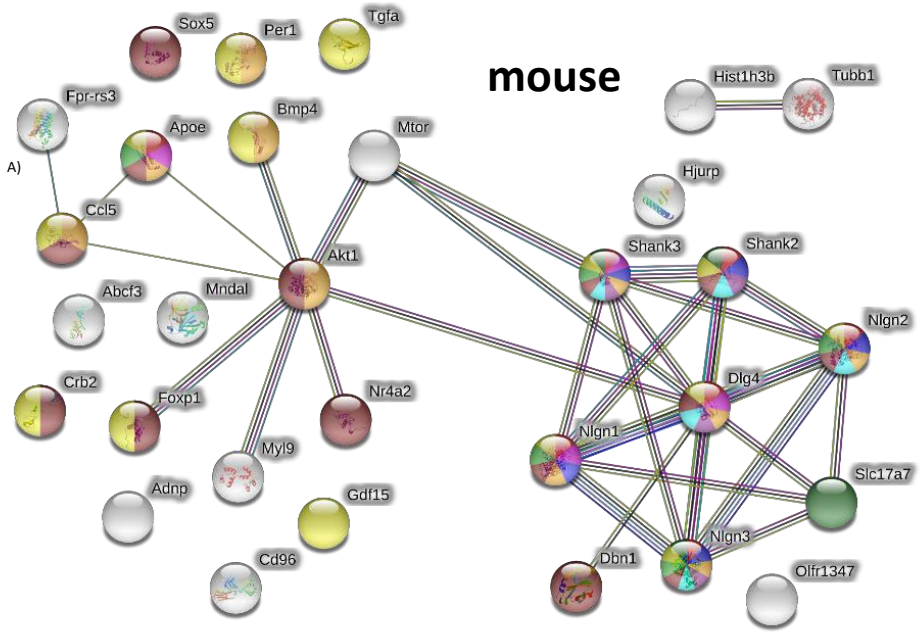
CP201 regulates dendritic spines formation and **maturation** through binding to microtubule end binding (EB) proteins

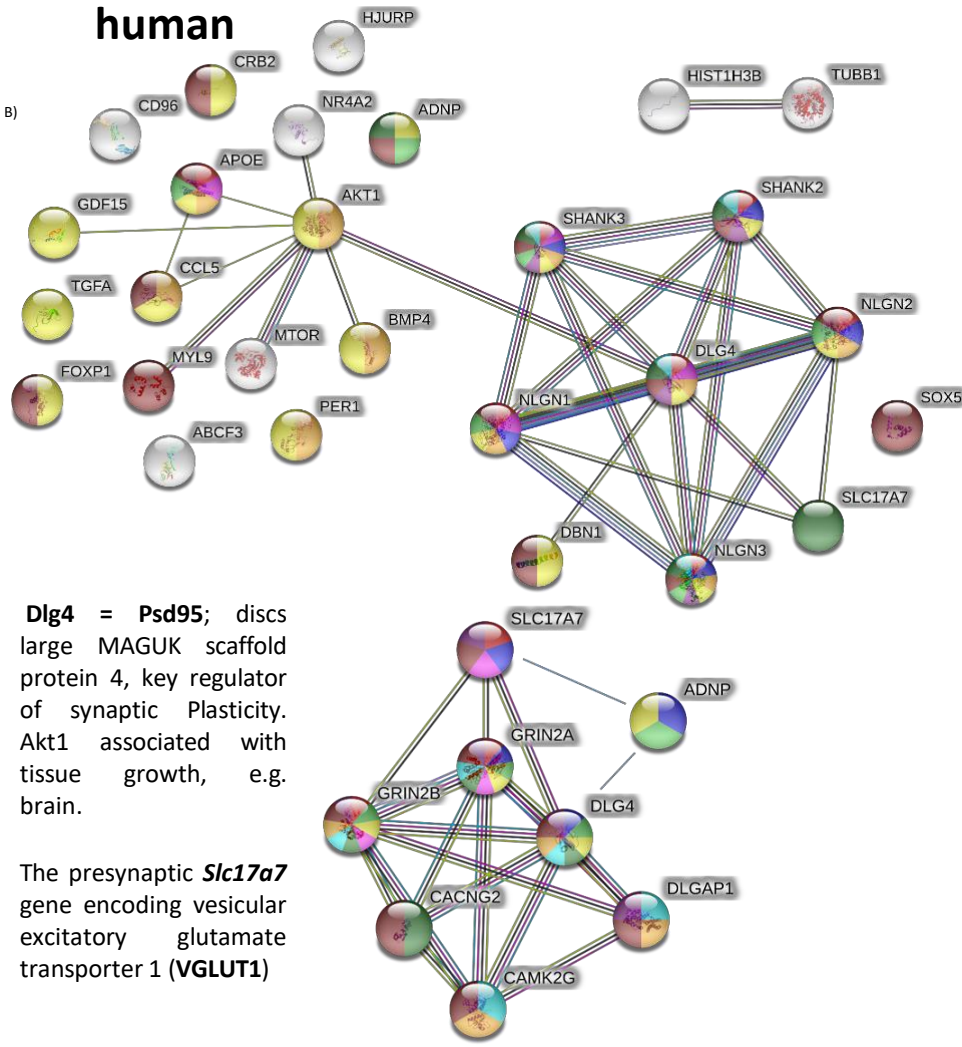
Activity-dependent neuroprotective protein deficiency models synaptic and developmental phenotypes of autism-like syndrome.

Hacohen-Kleiman G, Sragovich S, Karmon G, Gao AYL, Grigg I, Pasmanik-Chor M, Le A, Korenková V, McKinney RA, **Gozes I**.

J Clin Invest. 2018 Nov 1;128(11):4956-4969

Function Enrichment and Network Analysis Regulated by Genotype and Drug





Biological Process color legend	mouse	human
Synapse assembly	8.23E-10	6.72E-09
Positive regulation of synaptic transmission, glutamatergic	4.76E-08	3.26E-08
Regulation of synapse organization	5.91E-05	1.85E-06
Regulation of cell communication	7.15E-05	6.29E-07
AMPA glutamate receptor clustering	4.23E-08	8.29E-09
Learning or memory	0.00841	4.32E-05
Social behavior	1.75E-06	6.24E-05
Regulation of ion transport	4.91E-07	6.16E-07
Vocalization behavior	6.54E-07	1.22E-06
Nervous system development	4.22E-06	4.12E-06

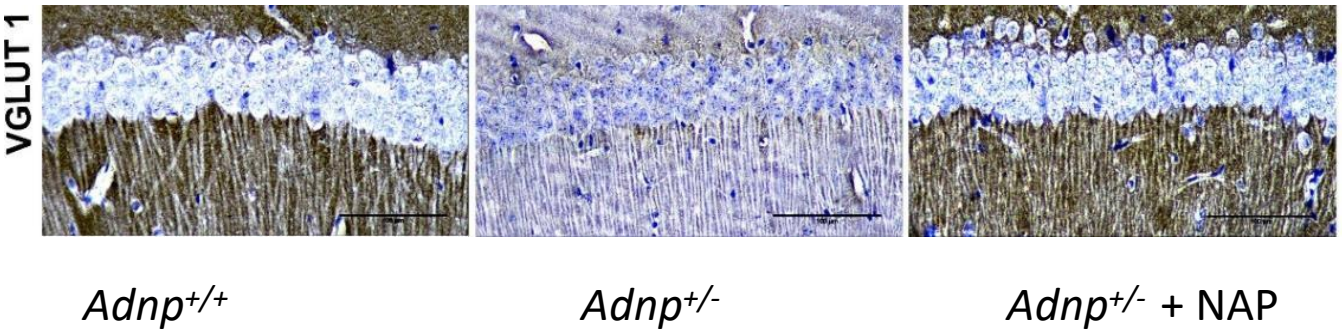
Dlg4 = Psd95; discs large MAGUK scaffold protein 4, key regulator of synaptic Plasticity. Akt1 associated with tissue growth, e.g. brain.

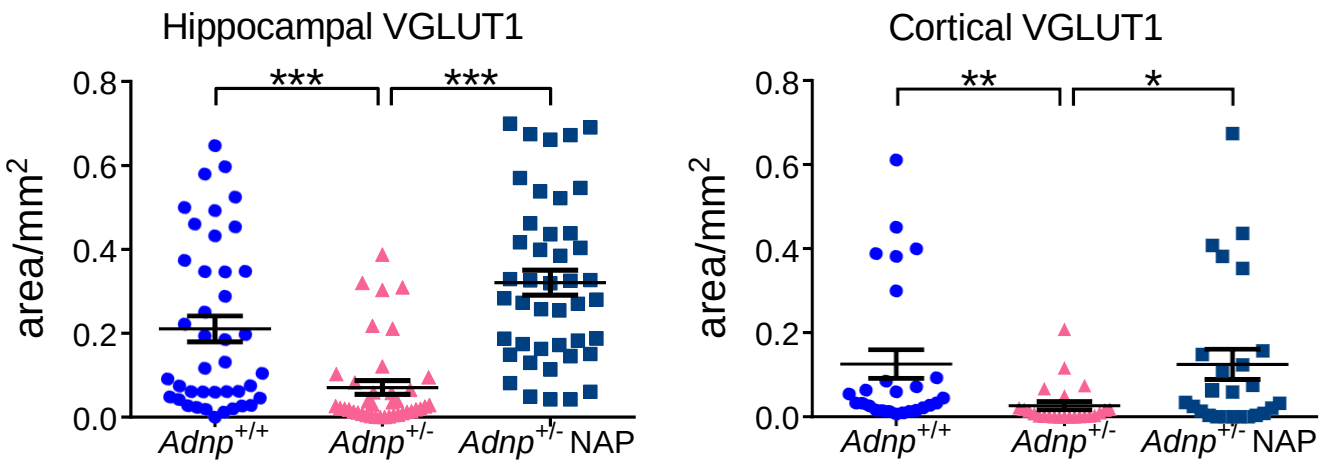
The presynaptic ***Slc17a7*** gene encoding vesicular excitatory glutamate transporter 1 (**VGLUT1**)

Hacohen-Kleiman G, Sragovich S, Karmon G, Gao AYL, Grigg I, Pasmanik-Chor M, Le A, Korenková V, McKinney RA, **Gozes I**.
J Clin Invest. 2018 Nov 1;128(11):4956-4969

Sragovich S, Malishkevich A, Piontkewitz Y, Giladi E, Touloumi O, Lagoudaki R, Grigoriadis N, **Gozes I**.
Transl Psychiatry. 2019 Jan 15;9(1):2.

ADNP/NAP Regulate the Excitatory Glutamatergic Synapse.



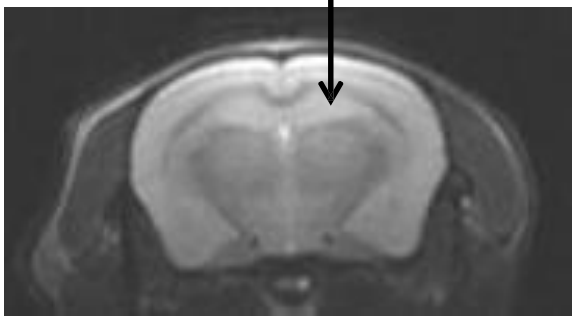


[The autism/neuroprotection-linked ADNP/NAP regulate the excitatory glutamatergic synapse.](#)
Sragovich S, Malishkevich A, Piontkewitz Y, Giladi E, Touloumi O, Lagoudaki R, Grigoriadis N, **Gozes I**.
Transl Psychiatry. 2019 Jan 15;9(1):2.

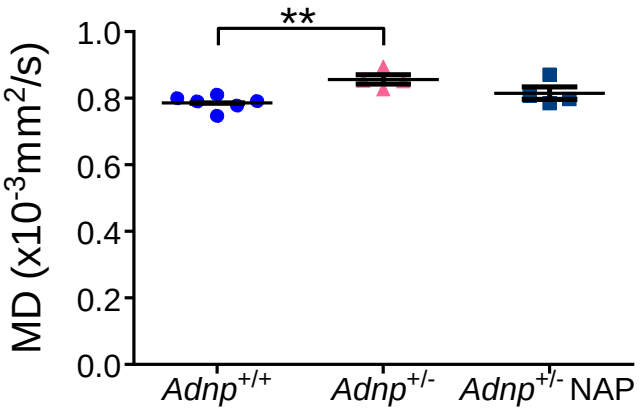
ADNP$^{+/-}$: Synapse Deficiency Reversed by NAP (CP201): Diffusion Tensor Imaging (DTI)

A)

Hippocampus
-1.84 from Bregma

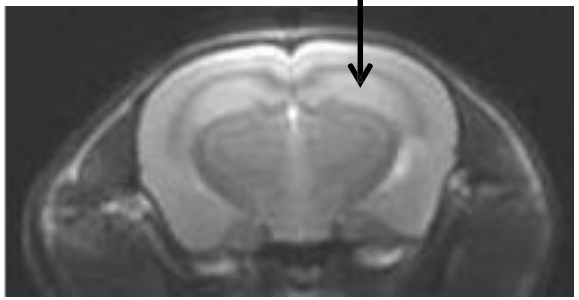


Mean Diffusivity (MD)

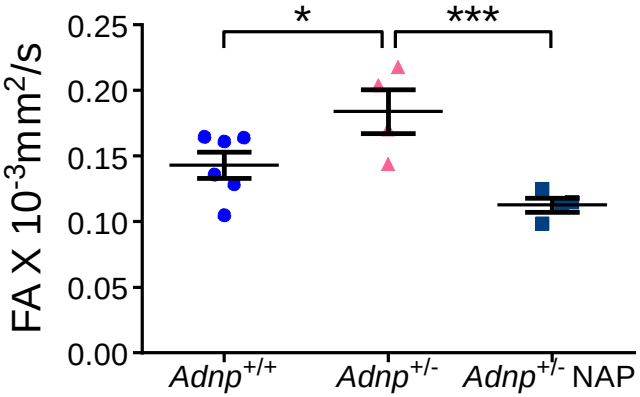


B)

Hippocampus
-2.34 from Bregma



Fractional Anisotropy (FA)



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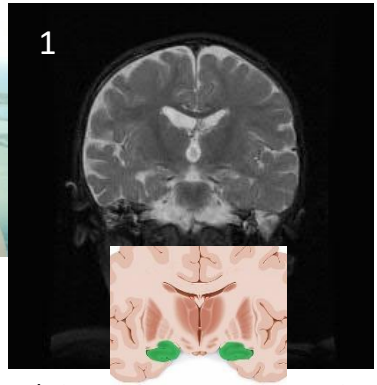
ADNP Syndrome Most Prevalent Mutation: p.Tyr719* (~20% of Children) *Motor and Cognitive Development*



Incomplete hippocampal inversion - an anatomic pattern whereby the hippocampus is more rounded, vertical and medially positioned than normal. Mild generalized cerebral volume loss with reduced posterior white matter (volumetric T2-MRI).

AD findings were craniofacial asymmetries, global developmental delay, autistic behaviors and slow thriving as she gradually matures. **AD began walking at 3.5 years.** AD is non-verbal, communicating with signs and word approximations. She continues to make slow but forward developmental progress

Ref:
Frontiers in Endocrinology, May 2017,
https://doi.org/10.3389/fendo.2017.00107

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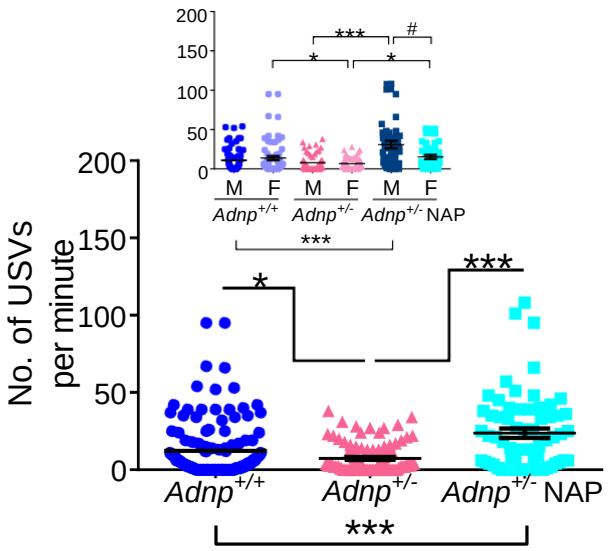
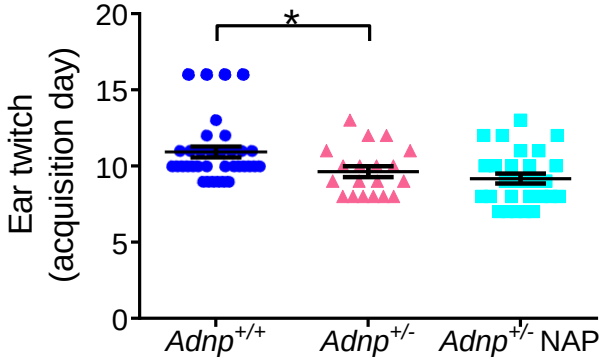
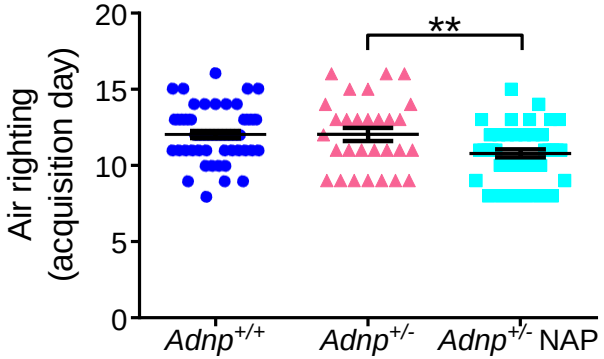
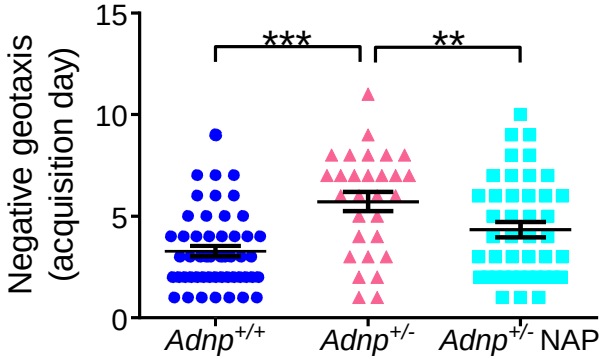
Adnp Haploinsufficiency Significantly Decreases Ultrasonic Vocalizations and Delays Developmental Milestones: NAP Corrects









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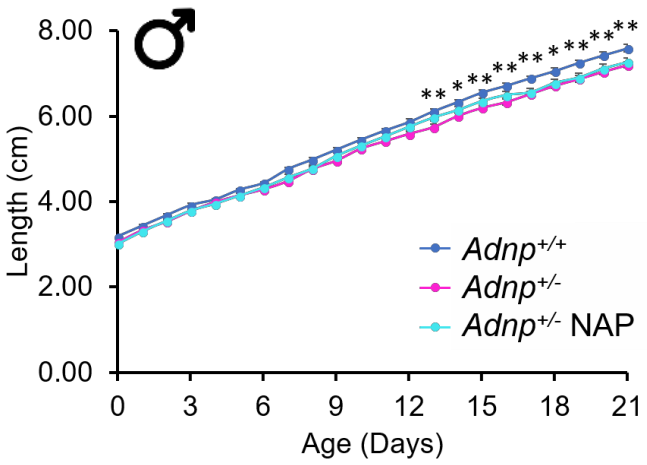
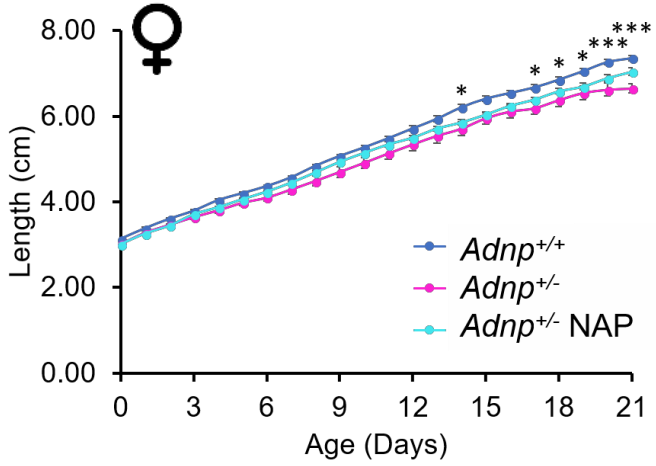
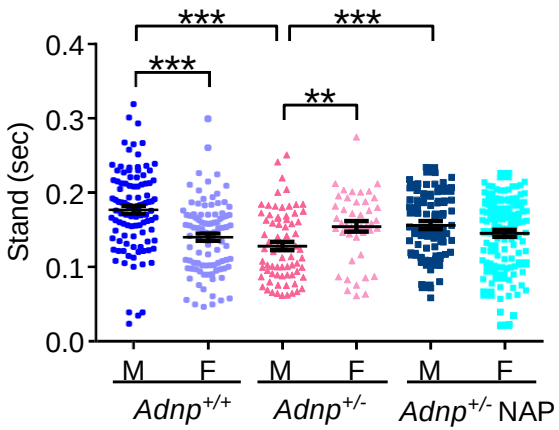
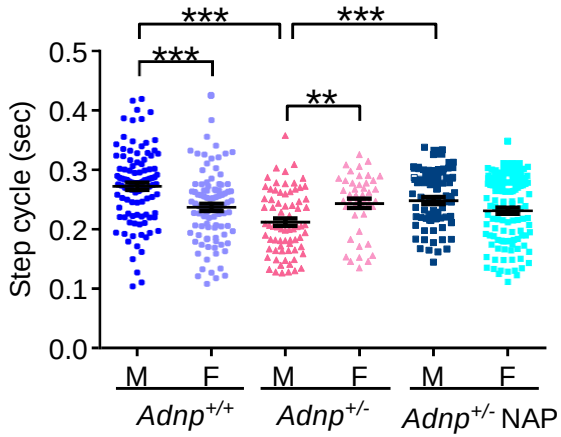
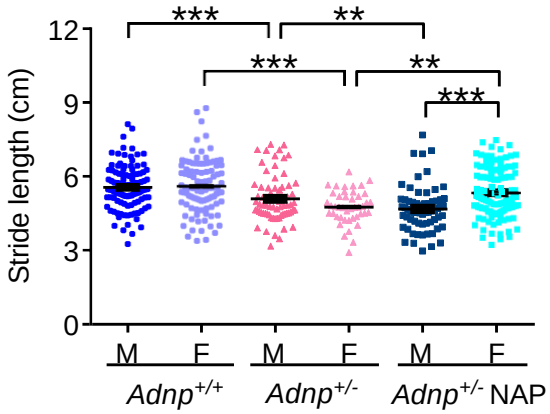
Adnp$^{+/-}$ Pups - Delayed Growth and Impaired Gait (18-40 days of age): Affected by NAP, in a Sex-Dependent Manner.



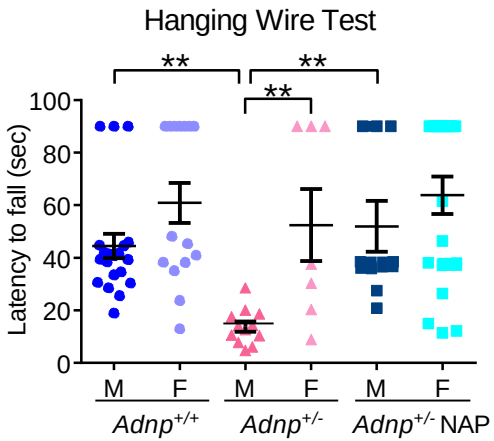


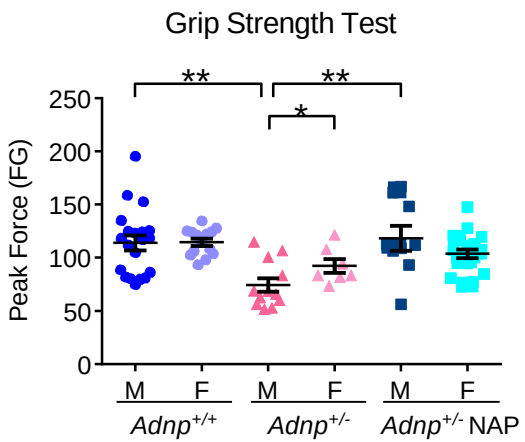


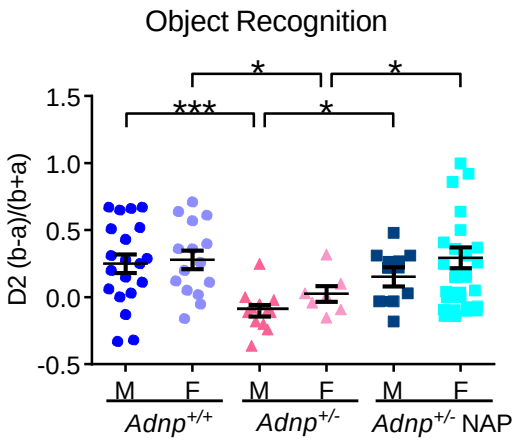


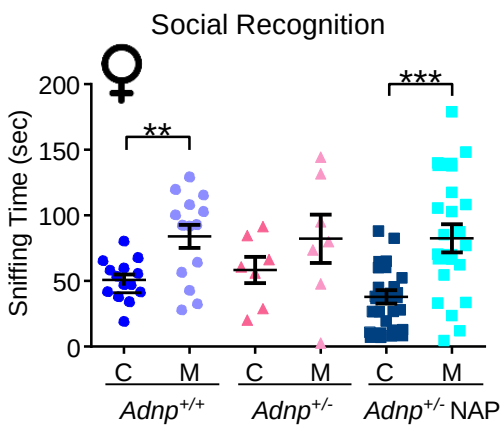


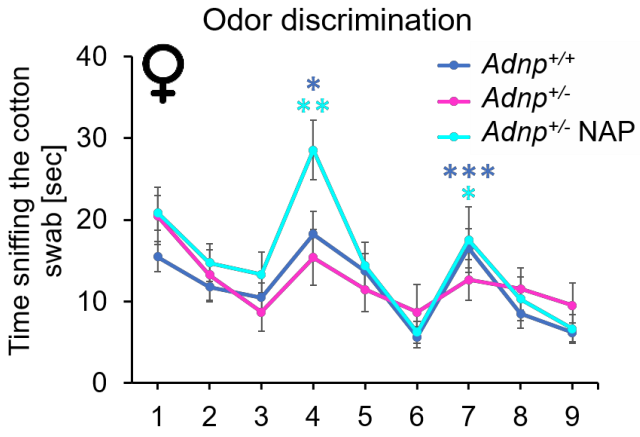
The *Adnp* genotype Affects Motor, Memory, and Social Aspects: Improvement by NAP Treatment.

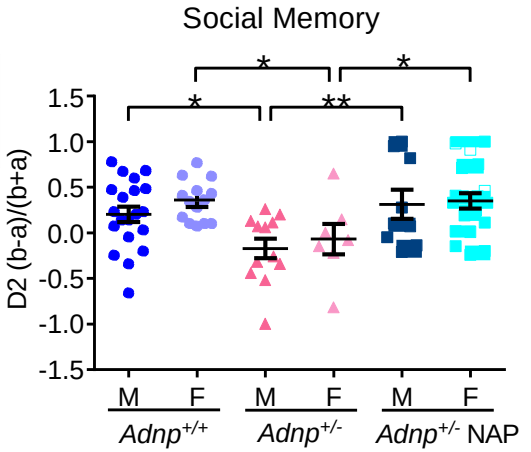












Hacohen-Kleiman G, Sragovich S, Karmon G, Gao AYL, Grigg I, Pasmanik-Chor M, Le A, Korenková V, McKinney RA, **Gozes I**. J Clin Invest. 2018 Nov 1;128(11):4956-4969

From Mouse to Human and Back: Drug Development

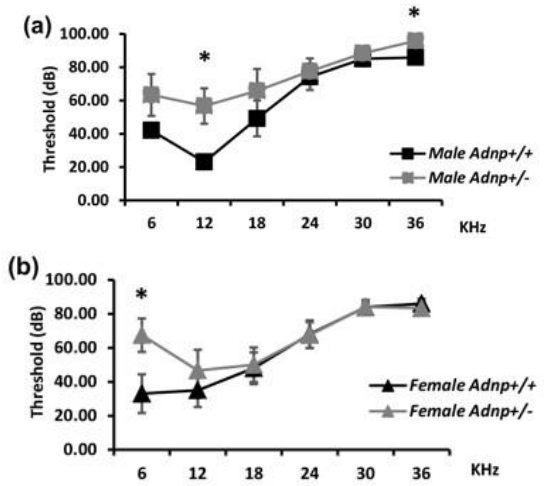
Trait	Adnp$^{+/-}$ Mouse	NAP efficacy	Patients with ADNP syndrome
Cognitive impairments	Morris water maze[1]; object recognition and social memory[2,3]	+[1] +	All inspected thus far show cognitive impairments[4,5]
Speech impediments	Vocalization	+	All have delays in language acquisition[4,6] and some do not speak at all[5]
Global developmental delays	Delayed air righting reflex	+	Global developmental delay (e.g. [5]), vision problems (e.g. delayed visual maturation)[6]
Short stature	Reduced length		Short stature[7]
Increased touch sensitivity	Ear twitch reflex develops earlier		Sensory processing problems[7]
Abnormal dentation	Delayed permanent teething[5]		Premature deciduous tooth eruption[5]
Motor impediments	Abnormal gait development, reduced grip strength, reduced capacity in the hanging wire test (males only)	+	Motor dysfunction/impaired development is shared by the children, as part of the global developmental delay[5]
Synaptic structural alterations	Reduced synaptic density, increase in immature shaft synapses (hippocampus)	+	Structural brain abnormalities[6], e.g. hippocampus[5]
Gene expression patterns	Dysregulation of splenic Abcf3, Adnp, Akt1, Bmp4, Cdh17, Iba1 (Aif1), Klf1, Mtor and Per1	+	Dysregulation of lymphoblastoid ABCF3, ADNP, AKT1, BMP4, CDH17, IBA1 (AIF1), KLF1, MTOR and PER1

The *Adnp* genotype Affects:

Hearing

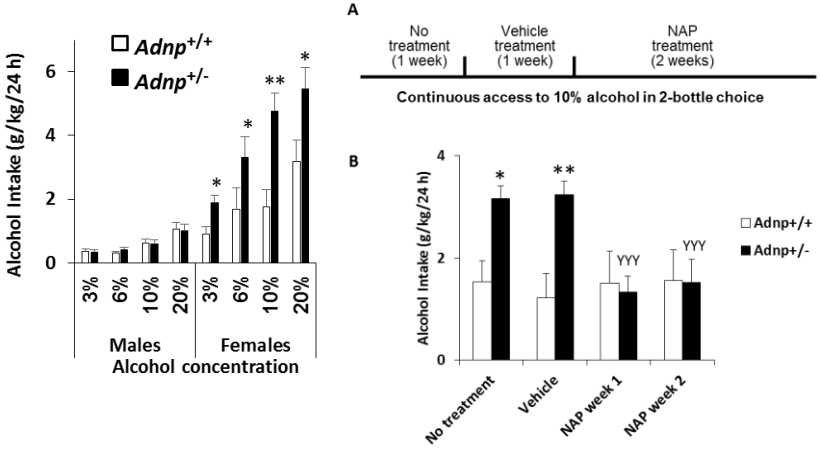
Alcohol Consumption – NAP repairs

Skin Thickness – NAP repairs



Atypical Auditory Brainstem Response and Protein Expression Aberrations Related to ASD and Hearing Loss in the Adnp Haploinsufficient Mouse Brain.

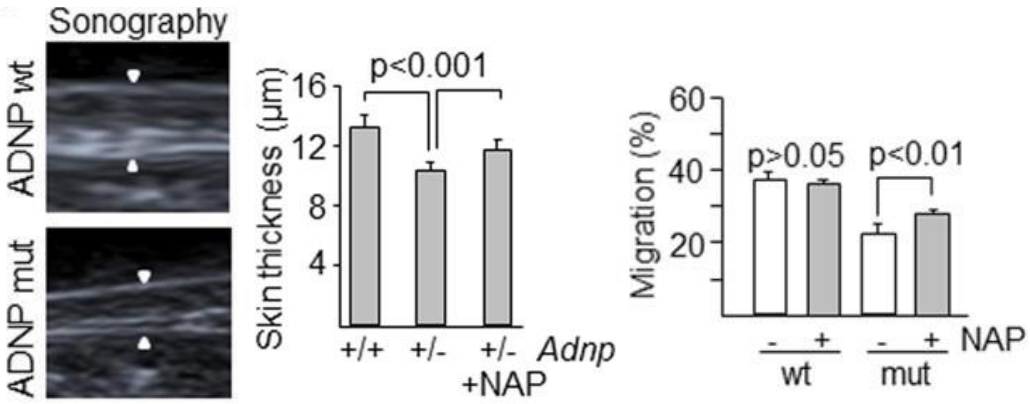
Hacohen-Kleiman G[1], Yizhar-Barnea O[2], Touloumi O[3], Lagoudaki R[3], Avraham KB[2], Grigoriadis N[3], Gozes I[4]. Neurochem Res. 2019 Jan 18. doi: 10.1007/s11064-019-02723-6. [Epub ahead of print]



Activity-dependent neuroprotective protein (ADNP) is an alcohol-responsive gene and negative regulator of alcohol consumption in female mice.

Ziv Y, Rahamim N, Lezmy N, Even-Chen O, Shaham O, Malishkevich A, Giladi E, Elkon R, **Gozes I**, Barak S. Neuropsychopharmacology. 2019 Jan;44(2):415-424. doi: 10.1038/s41386-018-0132-7. Epub 2018 Jun 27.

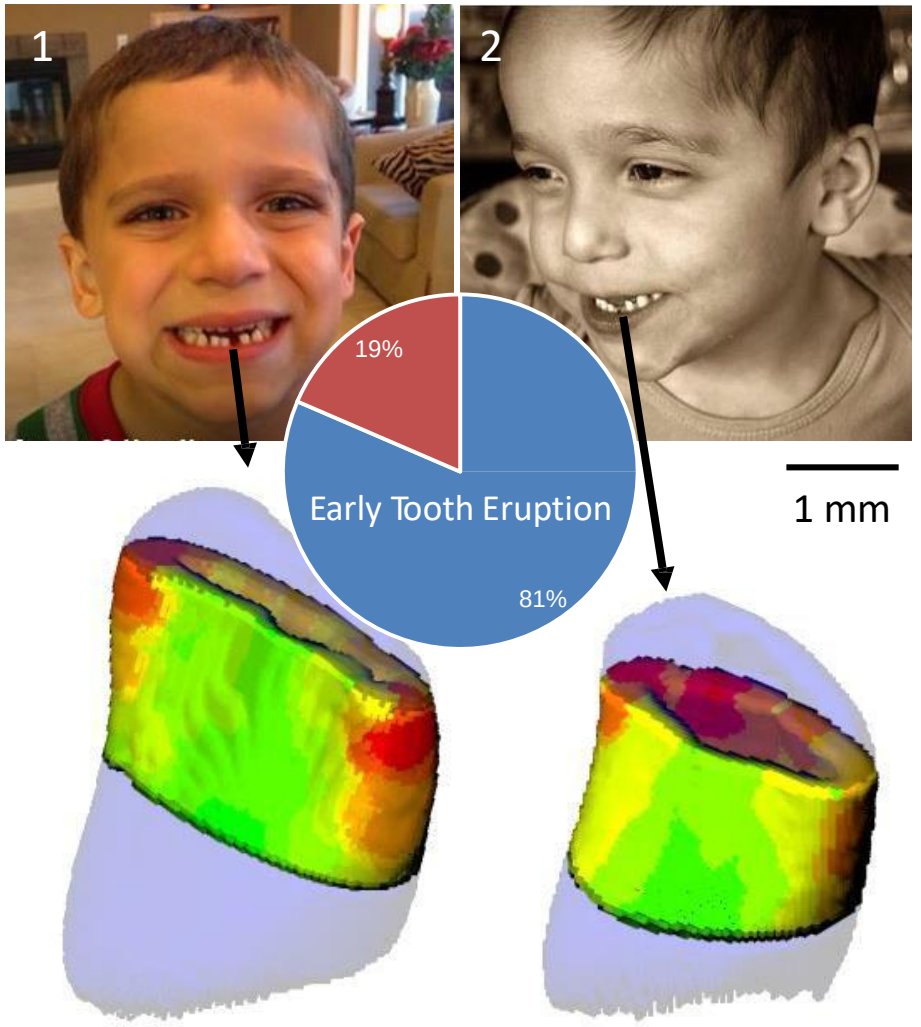
The transcription factor AP2 beta (TFAP2b), which is downregulated by chronic alcohol exposure had a 3.8-fold increased expression in female *Adnp*$^{+/-}$ mice, and in contrast, a 5-fold decreased expression in male *Adnp*$^{+/-}$ mice (hippocampus), as compared to sex-matched Adnp$^{+/+}$ controls. **Neuropsychopharmacology**. **2019 Jan;44(2):415-424**



From human to mouse and back to human

Cellular and animal models of skin alterations in the autism-related ADNP syndrome.

Mollinedo P, Kapitansky O, Gonzalez-Lamuño D, Zaslavsky A, Real P, **Gozes I**, Gandarillas A, Fernandez-Luna JL. Sci Rep. 2019 Jan 24;9(1):736. doi: 10.1038/s41598-018-36859-2.



[Premature primary tooth eruption in cognitive/motor-delayed ADNP-mutated children. Gozes I, Van Dijck A, Hacohen-Kleiman G, Grigg I, Karmon G, Giladi E, Eger M, Gabet Y, Pasmanik-Chor M, Cappuyns E, Elpeleg O, Kooy RF, Bedrosian-Sermone S. Transl Psychiatry. 2017 Feb 21;7(2):e1043. doi: 10.1038/tp.2017.27.

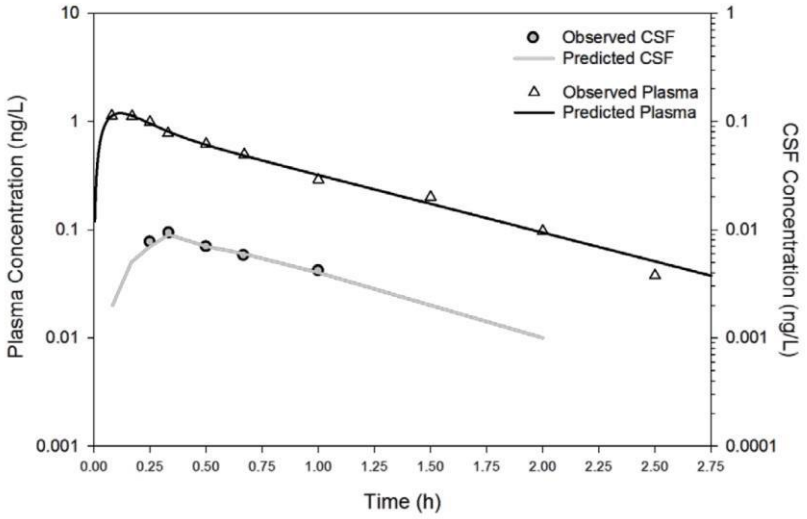
TEL AVIV UNIVERSITY אוניברסיטת תל אביב

Previous Clinical Studies

- – Phase I Safety Studies
  - Multiple intranasal and intravenous safety administration studies in adults revealed no significant side effects.
- – Phase IIa Efficacy Study in aMCI (Amnestic Mild Cognitive Impairment)
  - 16 weeks, 144 Patient, US multicenter clinical trial
  - Cognitive functions tested
  - **Statistically significant and durable impact found on visual working memory and short-term memory**
- – Phase IIa Efficacy Study in CIAS
  - 12 weeks, 66 patients, US multicenter trial run by the TURNS consortium
  - **Statistically significant Cognitive effects demonstrated on visual working memory, verbal memory**
  - **Statistically significant improvement in daily living skills (UPSA Scale)**

From Allon Therapeutics to - CORONIS NEUROSCIENCES

Drug Candidate CP201 Safety, Daily Living Skills **CIAS Patients**

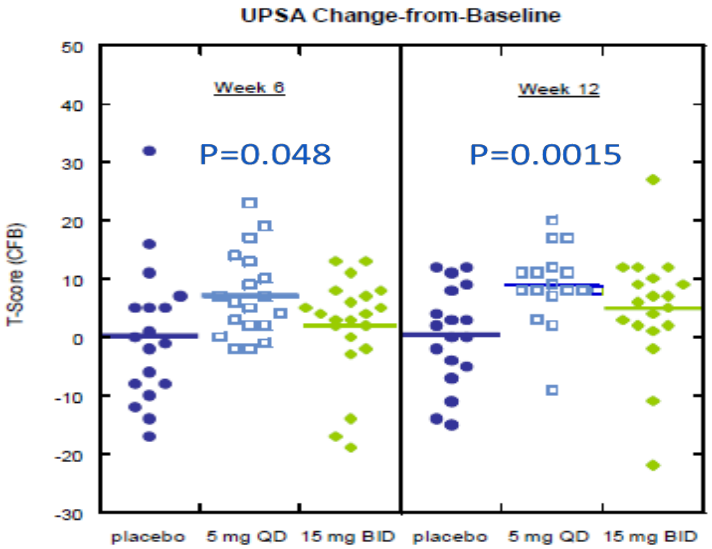


Safety & PK Studies

- Multiple intranasal and intravenous safety administration studies in adults revealed no significant side effects.
- CP201 is detectable in CSF (Penetrates BBB)

Clinical Efficacy Studies

- Cognitive effects demonstrated on visual working memory and verbal memory
- Improvement in daily living skills in Schizophrenic patients



Ref
Allon Therapeutics Inc. Professor Illana Gozes, Coronis CSO, Allon's Founder

Ref
Schizophr Res 136: 25-31.

CORONIS NEUROSCIENCES

Indication CP201 receives Orphan Drug Status

On February 22nd 2018 - CP201 (a.k.a Davunetide) has received an Orphan-Drug status for the treatment of ADNP Syndrome by the FDA Office of Orphan Products Development.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of davunetide is granted for *treatment of activity-dependent neuroprotective protein syndrome*.

Coronis Neurosciences' Team

Pre-IND Meeting September 4th, 2018

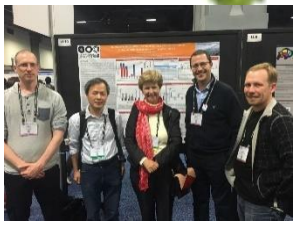
CORONIS NEUROSCIENCES

ERA-NET NEURON

מדינת ישראל
משרד הבריאות
Ministry of Health Israel

Thanks!

AMN
FOUNDATION



אוניברסיטת תל אביב
TEL AVIV UNIVERSITY

Adams Super Center for Brain Studies
Tel Aviv University

בית הספר סגול
למדעי המוח
אוניברסיטת תל אביב

Management Team Coronis Neurosciences

Dr. Eric Messika CEO

Hebrew University , **Ph.D.**

Herriot-Watt University, **MBA**

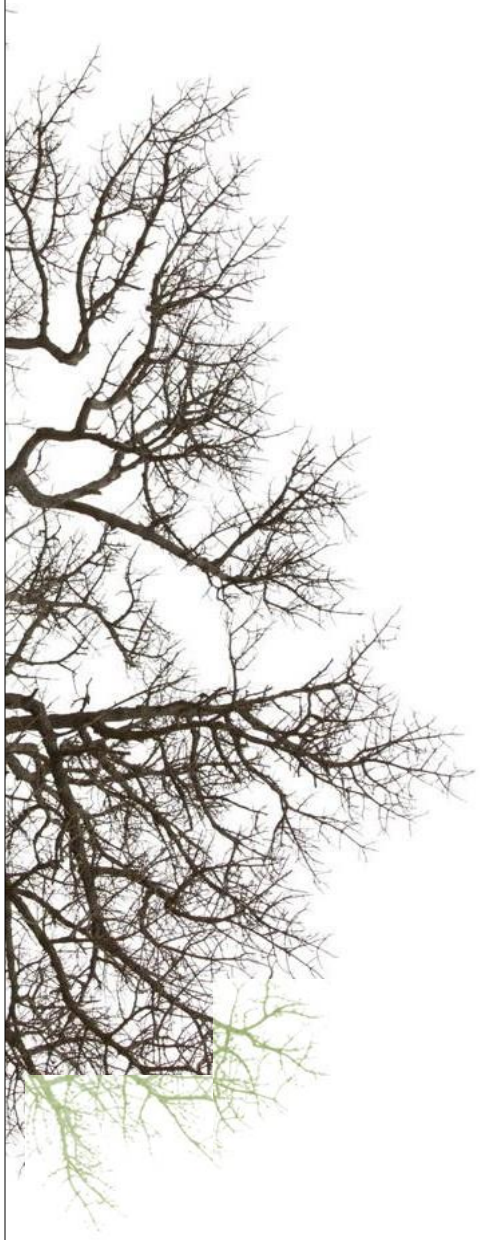
Prof. Illana Gozes CSO

Weizmann Institute of Science, **Ph.D.**

Professor, Tel Aviv University

Dr. Saar Oz VP Drug Development

Tel Aviv University, **Ph.D.**



CORONIS NEUROSCIENCES

Board of Directors Coronis Neurosciences

Mr. Udi Arad – Chairperson

More then 20 years experience in the High-Tech industry. Former Co-founder, President & CEO of Ex Libris, a high-growth High-Tech multinational software company.

Mr. Moshe Manor

CEO of Protalix Ltd. (NASDAQ:PLX). More than 30 years of Experience in the Bio-Pharmaceutical industry.

Mr. Ofer Haviv

President & CEO of Evogene Ltd. (NASDAQ:EVGN), Israel's leading Ag-Bio company. Previously served as the Director of Finance and Treasurer in Compugen (NASDAQ:CGEN).

Mr. Ittamar Givton

Managing Director of Automotive Equipment Group. Previously served as VP in Dor Energy, VP for Business Development In Dankner Investments and Deputy Director of the Budget Department in the Israeli Finance Ministry.

Champion of Hope – Science International 2016

https://www.facebook.com/ADNPkidsResearchFoundation/