News about the ADNP Syndrome

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Our Discovery: Activity-Dependent Neuroprotective Protein (ADNP)

Discovery of brain protective molecules

Disease \rightarrow Injury

Neuropeptides: VIP/PACAP \downarrow \downarrow

Brain support cell-derived protectants

Activity-Dependent Neuroprotective Protein

NAPVSIPQ

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

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**

Refs:
- 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.
The ADNP Gene Mutations: The ADNP Syndrome Affecting Neurodevelopment

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

ASD Prevalence¹
~9000 ADNP Patients

ASD Prevalence²
~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:
Translational Psychiatry (2017) 7, e1043
Front Endocrinol (Lausanne). 2017 May 19;8:107.
The NAP-Motif of Activity-Dependent Neuroprotective Protein (ADNP) Regulates Dendritic Spines through Microtubule End Binding (EB) Proteins

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

NAP enhances ADNP activity: Microtubule fortification

“Molecules that make our minds”
ADNP<sup>+/−</sup>: Synapse Deficiency Reversed by NAP (CP201)

Hippocampus – learning and memory

ADNP+/−: Synapse Deficiency Reversed by NAP (CP201)

Cerebral cortex – motor function

A) mGFP

Males

PSD95

Merge

Adnp+/+  Adnp+/−  Adnp+/− NAP

Spine Density (spines/μm)

Adnp+/+  Adnp+/−  Adnp+/− NAP

1.82±0.06  0.99±0.05  1.83±0.06

Shat Synapses/μm

Adnp+/+  Adnp+/−  Adnp+/− NAP

1.04±0.08  1.33±0.07  1.13±0.05

B) mGFP

Females

PSD95

Merge

Adnp+/+  Adnp+/−  Adnp+/− NAP

Spine Density (spines/μm)

Adnp+/+  Adnp+/−  Adnp+/− NAP

1.59±0.05  1.03±0.06  1.44±0.05

Shat Synapses/μm

Adnp+/+  Adnp+/−  Adnp+/− NAP

1.30±0.06  1.29±0.07  1.07±0.04

Drug Candidate CP201 MoA in vivo

ADNP-deficiency – synapse deficiency CP201 repairs

ADNP+/+

ADNP+/a−

ADNP−/−NAP

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.
Function Enrichment and Network Analysis Regulated by Genotype and Drug

Biological Process color legend
- Synapse assembly
- Positive regulation of synaptic transmission, glutamatergic
- Regulation of synapse organization
- Regulation of cell communication
- AMPA glutamate receptor clustering
- Learning or memory
- Social behavior
- Regulation of ion transport
- Vocalization behavior
- Nervous system development

mouse human

**Dlgs** = 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)


ADNP/NAP Regulate the Excitatory Glutamatergic Synapse.

ADNP<sup>+</sup>−−: Synapse Deficiency Reversed by NAP (CP201): Diffusion Tensor Imaging (DTI)

The autism/neuroprotection-linked ADNP/NAP regulate the excitatory glutamatergic synapse.
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:
Adnp Haploinsufficiency Significantly Decreases Ultrasonic Vocalizations and Delays Developmental Milestones: NAP Corrects

No. of USVs per minute

Ear twitch (acquisition day)

Air righting (acquisition day)

Negative geotaxis (acquisition day)

Adnp<sup>+/−</sup> 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.

**Hanging Wire Test**

**Grip Strength Test**

**Object Recognition**

**Social Recognition**

**Odor discrimination**

**Social Memory**

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<table>
<thead>
<tr>
<th>Trait</th>
<th>Adnp⁺/⁻ Mouse</th>
<th>NAP efficacy</th>
<th>Patients with ADNP syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairments</td>
<td>Morris water maze⁰; object recognition and social memory¹,²,³</td>
<td>+1 +</td>
<td>All inspected thus far show cognitive impairments⁴,⁵</td>
</tr>
<tr>
<td>Speech impediments</td>
<td>Vocalization</td>
<td>+</td>
<td>All have delays in language acquisition⁴,⁶ and some do not speak at all⁵</td>
</tr>
<tr>
<td>Global developmental delays</td>
<td>Delayed air righting reflex</td>
<td>+</td>
<td>Global developmental delay (e.g. ⁵), vision problems (e.g. delayed visual maturation)⁶</td>
</tr>
<tr>
<td>Short stature</td>
<td>Reduced length</td>
<td></td>
<td>Short stature⁷</td>
</tr>
<tr>
<td>Increased touch sensitivity</td>
<td>Ear twitch reflex develops earlier</td>
<td></td>
<td>Sensory processing problems⁷</td>
</tr>
<tr>
<td>Abnormal dentition</td>
<td>Delayed permanent teething⁵</td>
<td></td>
<td>Premature deciduous tooth eruption⁵</td>
</tr>
<tr>
<td>Motor impediments</td>
<td>Abnormal gait development, reduced grip strength, reduced capacity in the hanging wire test (males only)</td>
<td>+</td>
<td>Motor dysfunction/impaired development is shared by the children, as part of the global developmental delay⁵</td>
</tr>
<tr>
<td>Synaptic structural alterations</td>
<td>Reduced synaptic density, increase in immature shaft synapses (hippocampus)</td>
<td>+</td>
<td>Structural brain abnormalities⁶, e.g. hippocampus⁵</td>
</tr>
<tr>
<td>Gene expression patterns</td>
<td>Dysregulation of splenic Abcf3, Adnp, Akt1, Bmp4, Cdh17, Iba1 (Aif1), Klf1, Mtor and Per1</td>
<td>+</td>
<td>Dysregulation of lymphoblastoid ABCF3, ADNP, AKT1, BMP4, CDH17, IBA1 (AIF1), KLF1, MTOR and PER1</td>
</tr>
</tbody>
</table>
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.


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


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

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


From human to mouse and back to human
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 -
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
**Indication** CP201 receives Orphan Drug Status

On February 22\(^{nd}\) 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.


**Coronis Neurosciences’ Team**
Pre-IND Meeting September 4\(^{th}\), 2018
Thanks!
Management Team Coronis Neurosciences

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Board of Directors **Coronis Neurosciences**

**Mr. Udi Arad – Chairperson**
More than 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**

**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/