Gozes, I. (2017). *Xjenza Online*, 5:74–76.

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Commentary

Autism, Schizophrenia and Alzheimer's Disease: A Common Thread from Neuropeptides to Brain Regulating Genes

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Our original cloning of the gene coding for vasoactive intestinal peptide (VIP) (Bodner, Fridkin & Gozes, 1985), led to the identification of VIP's involvement in synapse formation and neuroprotection, through our discoveries of activity-dependent neurotrophic factor (ADNF) (Brenneman & Gozes, 1996) and activity-dependent neuroprotective protein (ADNP) (Bassan et al., 1999; Zamostiano et al., 2001). To precisely delineate VIP and ADNP activities in the whole animal, we established transgenic animals, showing that manipulating VIP content impacts cognition in the mouse (Gozes et al., 1993). As for mouse ADNP, complete knockout results in severe neuronal tube closure defects and embryonic death at the time of neural tube closure (Pinhasov et al., 2003). ADNP haploinsufficient mice survive and show cognitive and social deficiencies, with pathologies resembling autism (Malishkevich et al., 2015) and Alzheimer's disease (Vulih-Shultzman et al., 2007). Delineating the mechanism of action of ADNP, we discovered binding to the SWI/SNF chromatin remodeling complex and heterochromatin protein 1 alpha, and direct interaction with specific gene promoters (e.g. the major risk gene for Alzheimer's disease, apolipoprotein E) (Mandel & Gozes, 2007; Mandel, Rechavi & Gozes, 2007). We have further discovered interactions with proteins associated with RNA splicing (Schirer et al., 2014), as well as with proteins regulating translation, like eukaryotic initiation factor 4E (Eif4e) (Malishkevich et al., 2015). In the cell cytoplasm, ADNP further interacts with the autophagy mechanism, binding to microtubule associated protein 1 light chain 3 (LC3) (Merenlender-Wagner et al., 2015) and to microtubule end binding proteins (EBs) (Oz et al., 2014). These multiple interactions, with key regulatory proteins, was further associated with the fact that ADNP regulates $>$ 400 genes during embryonic development (Mandel et al., 2007) and thousands of genes postnatally, with age and sex differences (Amram et al., 2016). Importantly, ADNP was recently identified as one of the major genes mutated de novo, leading to autism (short review and case report, Gozes et al., 2015). Furthermore, blood borne ADNP levels correlate with IQ tests in elderly individuals (Malishkevich et al., 2016). To try and combat ADNP deficiencies, we have designed and synthesized an ADNP – derived peptide, drug candidate, NAP (NAPVSIPQ) (Bassan et al., 1999), also known as davunetide, CP201. Containing the EB1,3 interacting domain SIP, NAP directly interacts with microtubules to induce the formation of dendritic spines (Oz et al., 2014) and brain synaptic plasticity. While enhancing ADNP interaction with microtubules as well as the autophagosome, NAP provided enhanced microtubule dynamics and active autophagy (Esteves, Gozes & Cardoso, 2014; Merenlender-Wagner et al., 2014). In animals, NAP provided protection against neuronal toxicities and genetic manipulations associated with autism, schizophrenia (Vaisburd, Shemer, Yeheskel, Giladi & Gozes, 2015) and Alzheimer's disease (Matsuoka et al., 2008). Based on the NAP binding site, a novel drug candidate was developed, namely SKIP, enhancing axonal transport and protecting cognition (Amram et al., 2016). While SKIP development is still at the preclinical stage, NAP has shown clinical efficacy and is now planned for further clinical development at Coronis Neurosciences (http://www.coronisns.com/) (see Fig. 1).

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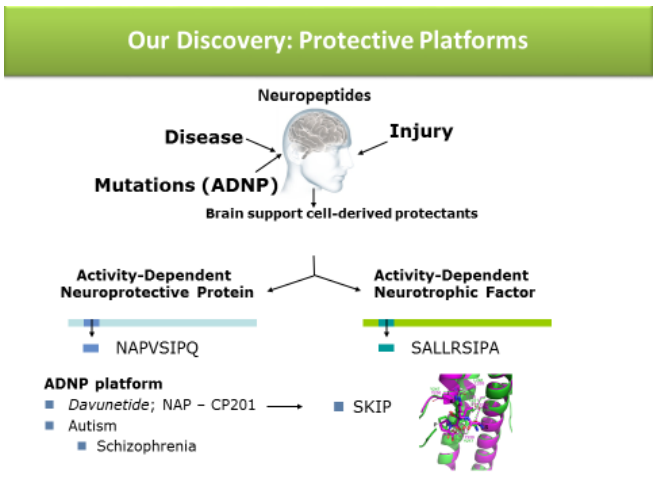

Figure 1: The figure describes our discoveries from neuropeptides (VIP) through the identification of ADNF and ADNP and novel protective peptides with a defined mechanism of action (docking on the microtubule end protein is shown) and clear clinical development path.

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References

Amram, N., Hacohen-Kleiman, G., Sragovich, S., Malishkevich, A., Katz, J., Touloumi, O., ... Gozes, I. (2016). Sexual divergence in microtubule function: the novel intranasal microtubule targeting SKIP normalizes axonal transport and enhances memory. *Psychiatry*, *21*, 1467–1476.

Bassan, M., Zamostiano, R., Davidson, A., Pinhasov, A., Giladi, E., Perl, O., ... Gozes, I. (1999). Complete sequence of a novel protein containing a femtomolar-activity-dependent neuroprotective peptide. *J Neurochem*, *72*, 1283–1293.

Bodner, M., Fridkin, M. & Gozes, I. (1985). Coding sequences for vasoactive intestinal peptide and PHM-27 peptide are located on two adjacent exons in the human genome. *Proc Natl Acad Sci U S A*, *82*, 3548–3551.

Brenneman, D. E. & Gozes, I. (1996). A femtomolar-acting neuroprotective peptide. *J Clin Invest*, *97*, 2299–2307.

Esteves, A. R., Gozes, I. & Cardoso, S. M. (2014). The rescue of microtubule-dependent traffic recovers mitochondrial function in Parkinson's disease. *Biochim Biophys Acta*, *1842*, 7–21.

Gozes, I., Glowa, J., Brenneman, D. E., McCune, S. K., Lee, E. & Westphal, H. (1993). Learning and sexual deficiencies in transgenic mice carrying a chimeric vasoactive intestinal peptide gene. *J Mol Neurosci*, *4*, 185–193.

Gozes, I., Helsmoortel, C., Vandeweyer, G., Van der Aa, N., Kooy, F. & Sermone, S. B. (2015). The Compassionate Side of Neuroscience: Tony Sermone's Undiagnosed Genetic Journey–ADNP Mutation. *J Mol Neurosci*, *56*, 751–757.

Malishkevich, A., Amram, N., Hacohen-Kleiman, G., Magen, I., Giladi, E. & Gozes, I. (2015). Activity-dependent neuroprotective protein (ADNP) exhibits striking sexual dichotomy impacting on autistic and Alzheimer's pathologies. *Psychiatry*, *5*, e501.

Malishkevich, A., Marshall, G. A., Schultz, A. P., Sperling, R. A., Aharon-Peretz, J. & Gozes, I. (2016). Blood-Borne Activity-Dependent Neuroprotective Protein (ADNP) is Correlated with Premorbid Intelligence, Clinical Stage, and Alzheimer's Disease Biomarkers. *J Alzheimers Dis*, *50*, 249–260.

Mandel, S. & Gozes, I. (2007). Activity-dependent neuroprotective protein constitutes a novel element in the SWI/SNF chromatin remodeling complex. *J Biol Chem*, *282*, 34448–34456.

Mandel, S., Rechavi, G. & Gozes, I. (2007). Activity-dependent neuroprotective protein (ADNP) differentially interacts with chromatin to regulate genes essential for embryogenesis. *Dev Biol*, *303*, 814–824.

Matsuoka, Y., Jouroukhin, Y., Gray, A. J., Ma, L., Hirata-Fukae, C., Li, H. F., ... Aisen, P. S. (2008). A neuronal microtubule-interacting agent, NAPVSIPQ, reduces tau pathology and enhances cognitive function in a mouse model of Alzheimer's disease. *J Pharmacol Exp Ther*, *325*, 146–153.

Merenlender-Wagner, A., Malishkevich, A., Shemer, Z., Udawela, M., Gibbons, A., Scarr, E., ... Gozes, I. (2015). Autophagy has a key role in the pathophysiology of schizophrenia. *Mol Psychiatry*, *20*, 126–132.

Merenlender-Wagner, A., Shemer, Z., Touloumi, O., Lagoudaki, R., Giladi, E., Andrieux, A., ... Gozes, I. (2014). New horizons in schizophrenia treatment: autophagy protection is coupled with behavioral improvements in a mouse model of schizophrenia. *Autophagy*, *10*, 2324–2332.

Oz, S., Kapitansky, O., Ivashco-Pachima, Y., Malishkevich, A., Giladi, E., Skalka, N., ... Gozes, I. (2014). The NAP motif of activity-dependent neuroprotective protein (ADNP) regulates dendritic spines through microtubule end binding proteins. *Mol Psychiatry*, *19*, 1115–1124.

Pinhasov, A., Mandel, S., Torchinsky, A., Giladi, E., Pittel, Z., Goldsweig, A. M., ... Gozes, I. (2003). Activity-dependent neuroprotective protein: a novel gene essential for brain formation. *Brain Res Dev Brain Res*, *144*, 83–90.

Schirer, Y., Malishkevich, A., Ophir, Y., Lewis, J., Giladi, E. & Gozes, I. (2014). Novel marker for the onset of frontotemporal dementia: early increase in activity-dependent neuroprotective protein (ADNP) in the face of Tau mutation. *PLoS One*, *9*, e87383.

Vaisburd, S., Shemer, Z., Yeheskel, A., Giladi, E. & Gozes, I. (2015). Risperidone and NAP protect cognition and normalize gene expression in a schizophrenia mouse model. *Sci Rep*, *5*, 16300.

Vulih-Shultzman, I., Pinhasov, A., Mandel, S., Grigoriadis, N., Touloumi, O., Pittel, Z. & Gozes, I. (2007). Activity-dependent neuroprotective protein snippet NAP reduces tau hyperphosphorylation and enhances learning in a novel transgenic mouse mode. *J Pharmacol Exp Ther*, *323*, 438–449.

Zamostiano, R., Pinhasov, A., Gelber, E., Steingart, R. A., Seroussi, E., Giladi, E., ... Gozes, I. (2001). Cloning and characterization of the human activity-dependent neuroprotective protein. *J Biol Chem*, *276*, 708–714.