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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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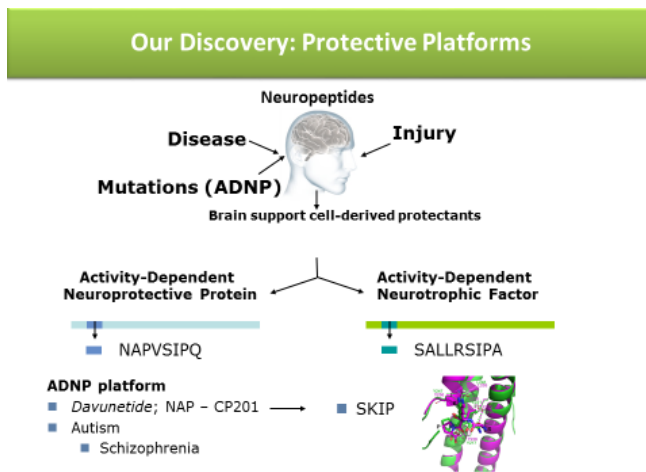


Figure 1: The figure describes our discoveries from neuropeptides (VIP) through the identification of ADNF and ADNP and novel protective peptides with a defined mechanism of action (docking on the microtubule end protein is shown) and clear clinical development path.

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