useful technique has only begun to be realized and will surely lead to novel insights into the complex regulation of gene expression.

FUNDING AND DISCLOSURE

John F Neumaier was supported by MH106532, MH106428, and DA035577 and a gift from the estate of Daniel Davis. Adam J Lesiak was supported by the training grant DA00007278.

Adam J Lesiak[1] and John F Neumaier[1]
[1]Department of Psychiatry and Behavioral Sciences, Harborview Medical Center, University of Washington, Seattle, WA, USA
E-mail: neumaier@uw.edu

Chandra R, Francis TC, Konkalmatt P, Amgalan A, Gancarz AM, Dietz DM *et al* (2015). Opposing role for Egr3 in nucleus accumbens cell subtypes in cocaine action. *J Neurosci* **35**: 7927–7937.

Doyle JP, Dougherty JD, Heiman M, Schmidt EF, Stevens TR, Ma G *et al* (2008). Application of a translational profiling approach for the comparative analysis of CNS cell types. *Cell* **135**: 749–762.

Heiman M, Schaefer A, Gong S, Peterson JD, Day M, Ramsey KE *et al* (2008). A translational profiling approach for the molecular characterization of CNS cell types. *Cell* **135**: 738–748.

Lesiak AJ, Brodsky M, Neumaier JF (2015). RiboTag is a flexible tool for measuring the translational state of targeted cells in heterogeneous cell cultures. *BioTechniques* **58**: 308–317.

Sanz E, Yang L, Su T, Morris DR, McKnight GS, Amieux PS (2009). Cell-type-specific isolation of ribosome-associated mRNA from complex tissues. *Proc Natl Acad Sci USA* **106**: 13939–13944.

Neuropsychopharmacology Reviews (2016) **41**, 374–376; doi:10.1038/npp.2015.262

Pharmacological Treatments for Autism Spectrum Disorder: Will Emerging Approaches Yield New Treatments?

Advances in modern genetics are rapidly changing the way we approach autism spectrum disorder (ASD) and other complex brain disorders. For example, massive sequencing efforts have identified over 50 'high confidence' genes that possess intrinsic diagnostic and predictive value for ASD (De Rubeis *et al*, 2014; Iossifov *et al*, 2014). A *post hoc* analysis reveals that these genes encode protein products that are primarily localized to post-synaptic boutons and are involved in synthesis of synaptic proteins. Preclinical studies have begun to stratify syndromic forms of autism into groups defined by varying degrees of excitatory/inhibitory imbalance. Importantly, the phenotypic overlap among these disorders has provided optimism that viable therapeutics might emerge that show efficacy in both monogenetic and idiopathic ASD populations due to similarly disrupted signaling pathways.

Perhaps the most well studied potential therapeutic mechanism is that of metabotropic glutamate receptor 5 ($mGlu_5$) antagonism in fragile X syndrome (FXS), where genetic and pharmacological strategies of reducing $mGlu_5$-dependent protein synthesis have shown robust preclinical efficacy. However, the failure of two phase 2 clinical trials has caused many to question whether the target is viable (Jacquemont *et al*, 2014). An alternative approach is use of the $GABA_B$ receptor agonist arbaclofen, which normalizes excessive protein synthesis and excitatory/inhibitory imbalance in FXS model mice. While a phase 2b clinical trial failed to achieve its primary endpoint of treating irritability, *post hoc* analysis with the Aberrant Behavior Checklist -Social Avoidance scale, a recently validated scale for the assessment of FXS, showed a treatment effect in the full study population. A *post hoc* subgroup of 27 subjects with more severe social impairment also showed improvements on the Vineland II socialization raw scores and on the Aberrant Behavior Checklist-Social Avoidance scale (Jacquemont *et al*, 2014).

Another ASD treatment strategy that is gathering momentum is the targeting of pleiotropic growth factors. In the case of Rett syndrome, small molecules mimicking the effects of brain derived neurotrophic factor or insulin-like growth factor 1 (IGF1) have efficacy in respiratory, cognitive and survival measures in preclinical studies (Castro *et al*, 2014; Kron *et al*, 2014). In fact, a recent trial concluded that recombinant human IGF1 improved respiratory and behavioral parameters in Rett syndrome patients, and patients are currently being recruited for phase 2b trials (Khwaja *et al*, 2014). Likewise, the IGF1 synthetic peptide, NNZ-2566, normalized spine density, hyperactivity and synaptic protein synthesis in a mouse model of FXS, and patients are currently being enrolled for phase 1 clinical trials (Deacon *et al*, 2015).

One common thread among these next generation ASD treatment strategies is that they normalize excitatory/inhibitory balance, in part, through the modulation of protein synthesis-dependent synaptic plasticity. These novel targets represent new access points to a pathway of genes disrupted in ASD patients, which may provide greater translational value than $mGlu_5$ antagonism. In addition, the recent failure of $mGlu_5$ modulators in FXS clinical trials does not invalidate the target, but rather highlights a need for a more complete understanding of the temporal, spatial and mechanistic subtleties underlying the inability of preclinical studies to translate to clinical populations, and the need to carefully consider patient stratification and appropriate outcome measures. Although it is too early to predict the ultimate impact of these advances on treatment of ASD, a renewed emphasis on these finer points of therapeutic design, coupled with the emergence of exciting new targets, represents important progress toward effective ASD treatments.

FUNDING AND DISCLOSURE

P Jeffrey Conn has been funded by NIH, Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, Michael J Fox Foundation, and Seaside Therapeutics. Over the past 3 years he has consulted for Pfizer, Cambridge, and has served on the Scientific Advisory Boards of Seaside Therapeutics, Michael J Fox Foundation, Stanley Center for Psychiatric Research Broad Institute (MIT/Harvard), Karuna Pharmaceuticals, Lieber Institute for Brain Development Johns Hopkins University, Clinical Mechanism (POCM) and Proof of Concept (POC) Consortium, and Neurobiology Foundation for Schizophrenia and Bipolar Disorder.

Rocco G Gogliotti declares no conflict of interest.

Rocco G Gogliotti[1,2] and P Jeffrey Conn[1,2]

[1]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA; [2]Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, TN, USA
E-mail: jeffrey.conn@Vanderbilt.Edu

Castro J, Garcia RI, Kwok S, Banerjee A, Petravicz J, Woodson J *et al* (2014). Functional recovery with recombinant human IGF1 treatment in a mouse model of Rett Syndrome. *Proc Natl Acad Sci USA* **111**: 9941–9946.

De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE *et al* (2014). Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* **515**: 209–215.

Deacon RM, Glass L, Snape M, Hurley MJ, Altimiras FJ, Biekofsky RR *et al* (2015). NNZ-2566, a novel analog of (1-3) IGF-1, as a potential therapeutic agent for fragile X syndrome. *Neuromolecular Med* **17**: 71–82.

Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D *et al* (2014). The contribution of de novo coding mutations to autism spectrum disorder. *Nature* **515**: 216–221.

Jacquemont S, Berry-Kravis E, Hagerman R, von Raison F, Gasparini F, Apostol G *et al* (2014). The challenges of clinical trials in fragile X syndrome. *Psychopharmacology* **231**: 1237–1250.

Khwaja OS, Ho E, Barnes KV, O'Leary HM, Pereira LM, Finkelstein Y *et al* (2014). Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome. *Proc Natl Acad Sci USA* **111**: 4596–4601.

Kron M, Lang M, Adams IT, Sceniak M, Longo F, Katz DM (2014). A BDNF loop-domain mimetic acutely reverses spontaneous apneas and respiratory abnormalities during behavioral arousal in a mouse model of Rett syndrome. *Dis Model Mech* **7**: 1047–1055.

Neuropsychopharmacology Reviews (2016) **41**, 376–377; doi:10.1038/npp.2015.259

Nicotine-Targeting Nano-Vaccines for Smoking Cessation

Nicotine addiction presents a well-recognized public health challenge and, in tobacco users, likely reflects a complex interplay of neurobehavioral, genetic, environmental, and social factors (Benowitz, 2010). This consideration makes it unlikely that any single medication or behavioral intervention can serve as a panacea to effectively reduce smoking behavior across the general population. It also highlights the need to optimize multiple treatment strategies that can be flexibly used, either alone or in combination, to blunt addiction-related effects of nicotine exposure.

Immunotherapeutic strategies (eg, nicotine vaccines) have been forwarded as an intriguing alternative or adjunct treatment approach to the use of pharmacological agents for smoking cessation (Pentel and LeSage, 2014). However, despite encouraging results early in development, the several conjugated nicotine vaccines that have been tested thus far have been relatively ineffective in clinical trials—modest increases in quit rates in smokers with relatively high levels of nicotine antibodies, and no effect in smokers with low antibody levels (Hatsukami *et al*, 2011). Although the reasons for such outcomes are undoubtedly complex, the limited positive results suggest that, to be successful, the immunogen must induce a sufficiently strong and reliably uniform nicotine-specific response.

Recent advances in vaccine development have led to innovative nano-vaccines that produce a more consistent immune response (and, presumably, improved efficacy), with reduced side effect liability. For example, the novel synthetic nano-vaccine SEL-068 has been reported to dose-dependently induce high affinity anti-nicotine antibody titers in both mice and non-human primates (Fraser *et al*, 2014). To further evaluate SEL-068, we conducted behavioral studies to determine how nicotine's discriminative-stimulus effects, which have been related to its subjective effects in humans (Smith and Stolerman, 2009), are modified by SEL-068 treatment in nicotine-naive and nicotine-trained monkeys. Results show that in the absence of other, non-specific behavioral effects, SEL-068: (a) effectively prevented the expression of nicotine's discriminable effects in nicotine-naïve monkeys and (b) produced a long-term (>25 weeks after vaccination) and substantive reduction (~6-fold) in the potency with which nicotine produced discriminable effects in nicotine-trained monkeys (Desai and Bergman, 2015). These are compelling results and provide the first evidence in a primate species that nicotine-targeting nano-vaccines can significantly reduce stimulus effects of nicotine that likely contribute to smoking behavior.

A key finding in our experiments was that SEL-068 was more effective against nicotine's discriminable effects in naïve than nicotine-experienced monkeys. These findings suggest that the degree of immunogenicity that is necessary for successful clinical outcomes may differ according to the subject's history of nicotine exposure. At present, it appears that nicotine nano-vaccines may be most useful as a preventative measure in non-exposed individuals—an ethically contentious matter—or, perhaps more realistically, in reducing the risk of relapse during long-term abstinence in former tobacco users. Conceivably, an improved nano-vaccine might produce an even stronger immune response to further reduce nicotine's discriminable and other addiction-related effects in nicotine-experienced subjects. Our results certainly support the continued development of novel nicotine nano-vaccines, either as a single approach or as a key element of a multimodal treatment strategy for smoking cessation.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank Selecta Biosciences (Watertown, MA) for providing SEL-068 as well as funds to support research involving SEL-068. Dr Desai's research on nicotine also is supported by K01-DA-031231 from NIDA/NIH. Dr Bergman also receives NIDA/NIH support for nicotine-related research under RO1-DA026892.

Rajeev I Desai[1] and Jack Bergman[1]

[1]Preclinical Pharmacology Laboratory (RID, JB), McLean Hospital/Harvard Medical School, Belmont, MA, USA
E-mail: rdesai@mclean.harvard.edu

Benowitz NL (2010). Nicotine addiction. *New Engl J Med* **362**: 2295–2303.

Desai RI, Bergman J (2015). Effects of the nanoparticle-based vaccine, SEL-068, on nicotine discrimination in squirrel monkeys. *Neuropsychopharmacology* **40**: 2207–2216.