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

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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.

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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

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Neurochips Enable Nanoscale Devices for High-Resolution *In Vivo* Neurotransmitter Sensing

The demand for new strategies to combat debilitating psychiatric and neurodegenerative diseases necessitates revolutionizing our approaches to investigate the connectivity and function of neural circuits. To elucidate how alterations in neuronal networks, which function at nanoscale synapses, contribute to brain-related disorders, it will be essential to monitor chemical neurotransmission *in vivo* at the length and timescales pertinent to intrinsically encoded information (Andrews, 2013). Nonetheless, current approaches for sensing neurotransmitters are far removed from these scales needed to decode chemical information processing in neurocircuitry.

To address the challenges of designing ultra-small, fast, highly selective, and multiplexed biosensors, we are investigating aptamers, which have emerged as alternatives to antibodies for molecular recognition. Aptamers are synthetic single-stranded DNA or RNA sequences that fold into unique three-dimensional structures to effect specific interactions with binding targets. Yet despite their promise, the elucidation of these rare nucleotide sequences is impeded by difficulties associated with producing screening substrates having highly controlled surface chemistries and characteristics (Vaish *et al*, 2010). Aptamers with picomolar to femtomolar dissociation constants exist but they are limited to sequences that recognize molecules significantly larger than neurotransmitters. To unleash the full potential of aptamers for *in vivo* neurotransmitter biosensing, we have invested a decade of research aimed at developing materials that enable high-affinity interactions between neurotransmitters tethered to optimized biospecific surfaces and nucleic acid libraries.

These substrates, termed 'neurochips', are fabricated so as to create enhanced environments for molecular recognition by controlling essential parameters and reducing nonspecific binding (Figure 1). Neurochips selectively capture large biomolecule binding partners including antibodies, native G-protein-coupled receptors

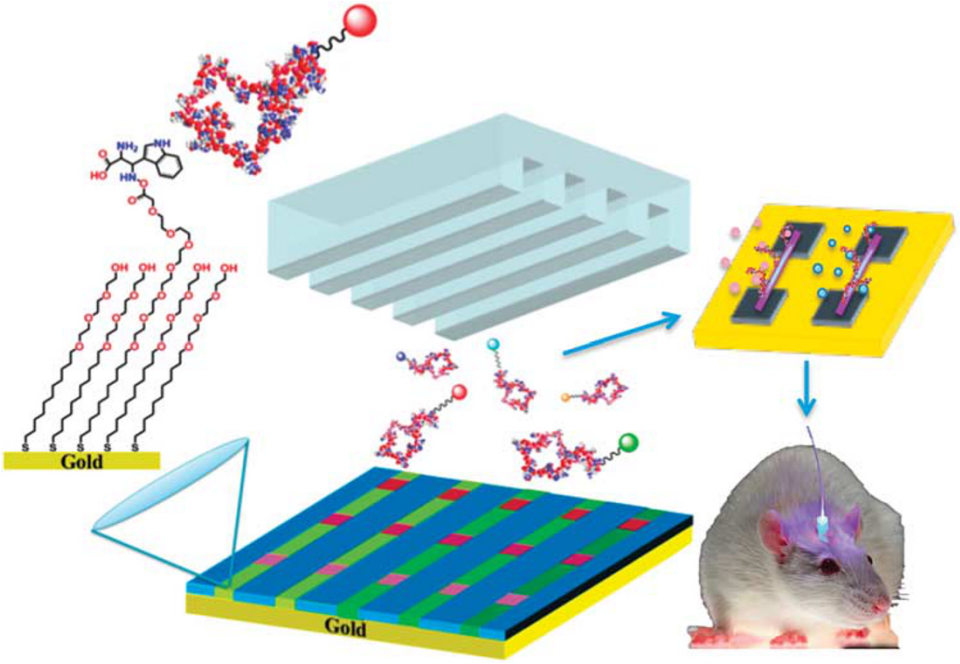

Figure 1. Schematic (not to scale) showing the chemistry, patterning, and use of neurochips to identify rare nucleotide sequences (aptamers) for use as neurotransmitter recognition elements in novel sensing devices to monitor chemical neurotransmission. (Left) The chemistry of self-assembled alkanethiols on gold substrates is shown. A small percent of these molecules is functionalized with 5-hydroxytryptophan (or other precursors/amino acids) to mimic free serotonin (or other neurotransmitters). (Middle) A neurochip patterned orthogonally via a microfluidics device is shown. This type of neurochip is used to screen large libraries of chemically synthesized nucleic acids to identify aptamer sequences that selectively recognize neurotransmitters. (Right) Aptamers are coupled to nanowire field-effect transistor devices for brain implantation and high-resolution *in vivo* neurotransmitter sensing.