Fraser CC, Altreuter DH, Ilyinskii P, Pittet L, LaMothe RA, Keegan M *et al* (2014). Generation of universal CD4 memory T cell recall peptide effective in humans and non-human primates. *Vaccine* **32**: 2896–2903.

Hatsukami DK, Jorenby DE, Gonzales D, Rigotti NA, Glover ED, Oncken CA *et al* (2011). Immunogenicity and smoking cessation outcomes for a novel nicotine immunotherapeutic. *Clin Pharmacol Ther* **89**: 392–399.

Pentel PR, LeSage MG (2014). New directions in nicotine vaccine design and use. *Adv Pharmacol* **69**: 553–580.

Smith JW, Stolerman IP (2009). Recognising nicotine: the neurobiological basis of nicotine discrimination. *Handb Exp Pharmacol* **192**: 295–333.

Neuropsychopharmacology Reviews (2016) **41**, 377–378; doi:10.1038/npp.2015.234

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

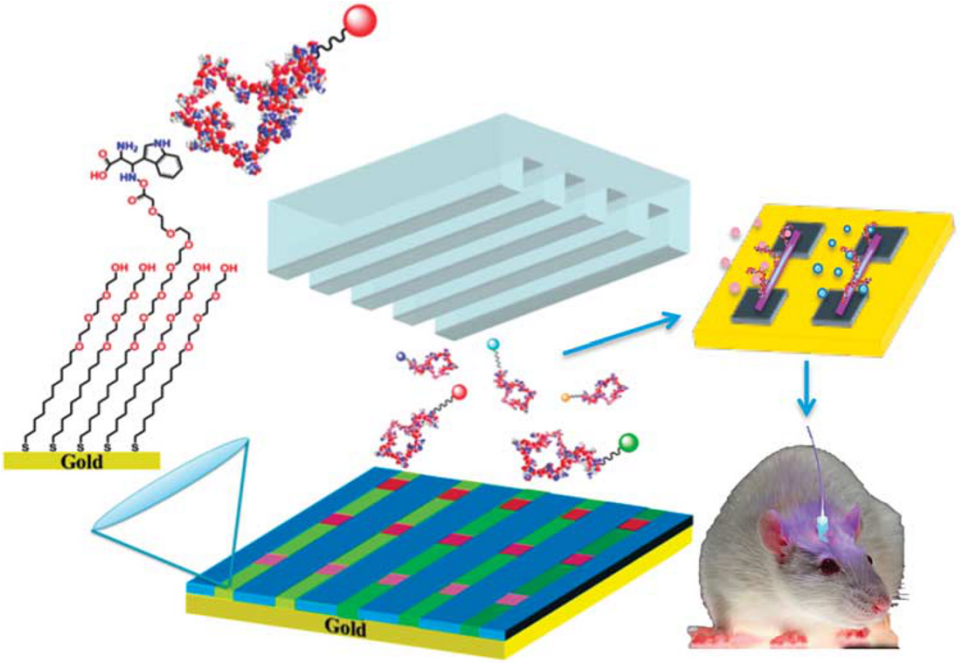

Figure 1. Schematic (not to scale) showing the chemistry, patterning, and use of neurochips to identify rare nucleotide sequences (aptamers) for use as neurotransmitter recognition elements in novel sensing devices to monitor chemical neurotransmission. (Left) The chemistry of self-assembled alkanethiols 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.

(Vaish *et al*, 2010), and nucleic acid aptamers. At present, we are using neurochips to identify rare nucleotides isolated from combinatorial libraries consisting of hundreds of billions of candidate sequences based on relative affinities for small-molecule neurotransmitter targets. We have also developed micro- to nanoscale surface patterning techniques (Liao *et al*, 2012) and used high-throughput microfluidics (Liao *et al*, 2013) to create multiplexed neurotransmitter substrates. A significant advantage of multiplexed patterning is the capacity to capture and to sort different neurotransmitter-specific aptamers side-by-side while providing opportunities to determine and to compare *in situ* binding affinities.

The discovery of neurotransmitter aptamers will enable their functional integration into nanometer-diameter field-effect transistor (FET) nanowires, which will function as neurotransmitter recording elements (Figure 1). Devices patterned with aptamer-modified FETs will be used to carry out dynamic *in vivo* monitoring of neurotransmission with response times on the order of milliseconds (or faster) (Kim *et al*, 2015). When combined with appropriate passivation to suppress biofouling, microsensors that detect dopamine with sub-second temporal resolution have been shown to function over months *in vivo* in rats and mice (Clark *et al*, 2010). Thus, neurochips will enable the development of devices that will advance the understanding of the roles of small-molecule neurotransmitters in the complex landscape of brain interneuronal communication and dysfunction. Unraveling the emergent properties of integrated chemical neurotransmission associated with neural circuits using this approach will be advantageous for uncovering processes associated with cognition, emotion, and learning and memory.

FUNDING AND DISCLOSURE

During the past 3 years, AMA has received compensation from Forest Laboratories (Actavis) for work as a consultant and from the American Chemical Society for work as Associate Editor of ACS Chemical Neuroscience, in addition to income from her primary employer (University of California, Los Angeles). NN declares that, except for graduate student stipends received from the University of California, Los Angeles, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

ACKNOWLEDGMENTS

Funding from the CalBRAIN Neurotechnology Program and the Shirley and Stefan Hatos Foundation are gratefully acknowledged.

Nako Nakatsuka[1] and Anne M Andrews[1,2]

[1]Department of Chemistry and Biochemistry, and California NanoSystems Institute, University of California, Los Angeles, CA, USA; [2]Department of Psychiatry & Biobehavioral Health, Semel Institute for Neuroscience and Human Behavior, and Hatos Center for Neuropharmacology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

E-mail: aandrews@mednet.ucla.edu

Andrews AM (2013). The BRAIN initiative: toward a chemical connectome. *ACS Chem Neurosci* **4**: 645.

Clark JJ, Sandberg SG, Wanat MJ, Gan JO, Horne EA, Hart AS *et al* (2010). Chronic microsensors for longitudinal, subsecond dopamine detection in behaving animals. *Nat Methods* **7**: 126–129.

Kim J, Rim YS, Chen H, Cao HH, Nakatsuka N, Hinton HL *et al* (2015). Fabrication of high-performance ultrathin In_2O_3 film field-effect transistors and biosensors using chemical lift-off lithography. *ACS Nano* **9**: 4572–4582.

Liao WS, Cao HH, Cheunkar S, Shuster MJ, Altieri SC, Weiss PS *et al* (2013). Small-molecule arrays for sorting G-protein-coupled receptors. *J Phys Chem C* **117**: 22362–22368.

Liao WS, Cheunkar S, Cao HH, Bednar HR, Weiss PS, Andrews AM (2012). Subtractive patterning via chemical lift-off lithography. *Science* **337**: 1517–1521.

Vaish A, Shuster MJ, Cheunkar S, Singh YS, Weiss PS, Andrews AM (2010). Native serotonin membrane receptors recognize 5-hydroxytryptophan-functionalized substrates: enabling small-molecule recognition. *ACS Chem Neurosci* **1**: 495–504.

Neuropsychopharmacology Reviews (2016) **41,** 378–379; doi:10.1038/npp.2015.307

Closing the Loop in Deep Brain Stimulation for Psychiatric Disorders: Lessons from Motor Neural Prosthetics

Deep brain stimulation (DBS) is a promising technique for modulating circuits underlying mental illnesses, but has not done well in clinical trials (Dougherty *et al*, 2015). Advocates have argued that the trial failures arise from a need to better define the anatomic target for stimulation (Riva-Posse *et al*, 2014). This ignores a larger issue: DBS is an open-loop, static therapy. Patients' disorders, on the other hand, are not static. Symptoms change over hours to days, but DBS programming visits occur every 4–12 weeks. To resolve that mismatch, investigators are now pursuing 'closed-loop' DBS, where the device itself monitors patients' brain activity and self-titrates therapy to a desired endpoint (Figure 1). The challenge, however, is determining what to monitor. Verified neural biomarkers for psychiatric disorders remain elusive. Preliminary data suggest candidate markers (Widge *et al*, 2015), but they are far from the real-time algorithms needed for effective feedback-controlled DBS.

A different neuroscience community has had greater success in 'reading out' the brain: brain–computer interface (BCI) researchers. Their technologies 'decode' movement signals from the cortex, then convey movement goals to assistive devices. Closed-loop DBS researchers seek to do something similar, decoding a patient's emotional state. BCI investigators have uncovered two insights that could assist psychiatry's quest. First, encoding matters—decoding is better with a robust model of how cortical regions encode mental states. This matters for psychiatry, because disorders like depression and post-traumatic stress disorder are heterogeneous. Effective decoding may require identification of discrete