expression coupled with its involvement in multiple psychiatric and neurological illness place this receptor as a critical player in the understanding of CNS disorders.

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DISCLOSURE
The author was an employee of Pfizer (formerly Wyeth).

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Modeling Neuropsychiatric Disease-Relevant Human SNPs in Mice

Single nucleotide polymorphisms (SNPs) are variations in DNA sequence that occur when a single nucleotide in the genome is altered. These seemingly small variations can have a major impact on how humans respond to disease, environment, and drugs.

Gene targeting in mice has allowed the analysis of varied aspects of gene function in mammals. During the past decade, thousands of null, hypomorphic, and conditional alleles have been constructed. Gene targeting can also be used to generate point mutations in mice for those genes in which human SNPs have been identified. This approach, however, has not yet been widely used due, in part, to the labor-intensive procedures involved in building the complex targeting vectors required. Recent advances in 'recombineering' of bacterial artificial chromosome vectors have streamlined this process (Yu *et al*, 2000; Lee *et al*, 2001), making the use of 'knock-in' mice a natural progression for the development of mouse models to investigate human disease-related SNPs.

Neuropsychiatric diseases are dependent on multiple genetic and environmental determinants, and thus represent some of the greatest challenges for animal modeling. However, a few genes harboring specific SNPs have emerged as promising candidates. Among these, common SNPs in brain-derived neurotrophic factor (*Bdnf*), the μ-opioid receptor (*Oprm1*), and catechol-*O*-methyltransferase (*COMT*) have been modeled in mice using three unique approaches.

A common SNP in the *BDNF* gene (Val66Met) is associated with anatomical (hippocampal volume) and behavioral (performance in memory tasks) impairments in humans. To recapitulate the equivalent variant in mice, we made a point mutation (G196A) to change valine 66 to methionine. In addition to the expected phenotypes of decreased hippocampal volume and impaired context-dependent memory, these mice revealed a novel anxiety phenotype that had not yet been reported in humans (Chen *et al*, 2006).

A large number of studies have examined the *OPRM1* gene as a candidate for genetic contribution to the risk for substance dependence. The best-characterized polymorphism in this gene is a missense mutation in exon 1, involving an A–G substitution at position 118. Owing to the high sequence similarity between mouse and human at the nucleotide (86.9%), and amino-acid level (92.3%), a knock-in mouse was developed that possessed the mouse-equivalent SNP of the human A118G SNP in the murine *Oprm1* gene (Mague *et al*, 2009). In a complimentary approach, a second mouse line for this SNP was generated that expressed humanized receptors with and without the A118G variant (Ramchandani *et al*, 2010). Both models recapitulated some phenotypes observed in humans, clarified discrepancies regarding functional aspects of the receptor, and identified novel phenotypes.

A third approach to model human SNPs takes advantage of a biochemical phenotype associated with a polymorphism in the *COMT* gene (COMT-Val), which results in higher protein levels and enzyme activity compared with individuals expressing COMT-Met. However, several other common haplotypes in the *COMT* gene have been associated with similar biochemical effects. Therefore, to model this phenotype and clarify the specificity of the COMT-Val SNP, was generated a transgenic mouse that overexpressed the *COMT-Val* gene in the continued presence of the mouse *Comt1* gene (Papaleo *et al*, 2008). Phenotypes related to cognitive and stress reactivity in these transgenic mice were analogous to those reported in humans.

Modeling human SNPs in mice is important for a variety of reasons. In some cases the rationale might be to clarify inconsistencies associated with *in vitro* data, in others to provide more precise information on the specificity of the SNP, or to explore novel phenotypes. In all cases, these mice now allow for the determination of molecular mechanisms that mediate the behavioral consequences of these SNPs, and as such contribute to a better understanding of their significance in human disease.

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Cortical Circuits for Motor Control

Voluntary control of movement relies on activity in a subclass of layer 5B pyramidal neurons projecting to the spinal cord—corticospinal neurons (also called Betz cells or upper motor neurons) (Figure 1). In motor cortex, corticospinal neurons are one of the many classes of pyramidal neurons distributed over multiple layers and sublayers with diverse local and long-range projections. Studies in primates, the motor systems of which so closely resemble our own, have provided a wealth of information about the spiking activities of motor cortex neurons during action planning and execution. However, *in vivo* recording methods usually preclude identification of the precise laminar locations of neurons and their synaptic connectivity, and *in vitro* analysis is impractical in primates. Consequently, much remains to be learned about how local circuits are organized according to projection target and sublayer (Brown and Hestrin, 2009; Anderson *et al*, 2010), and how this organization influences spiking activity in different subclasses of projection neurons in motor cortex.

Recently, several groups have established the feasibility of motor behavior experiments with rodents, using not only electrophysiology, but with calcium imaging, also large-scale optical recordings (Dombeck *et al*, 2009). It is remarkable that this has now been combined with sophisticated within-session learning paradigms (Komiyama *et al*, 2010). There are, of course, limitations. One of the limitations is depth: only neurons in the upper layers of the cortex are easily imaged. However, this is hardly uninteresting, as microcircuit mapping studies have shown that layer 2/3 is the main source of synaptic output within motor cortex circuits, and is the major source of input to corticospinal neurons (Anderson *et al*, 2010).

Another intriguing issue is whether circuits in the remaining frontal agranular cortex—presumably involved in more 'cognitive' aspects of motor control—are organized in the form of primary motor cortex. If "thinking is the evolutionary internalization of

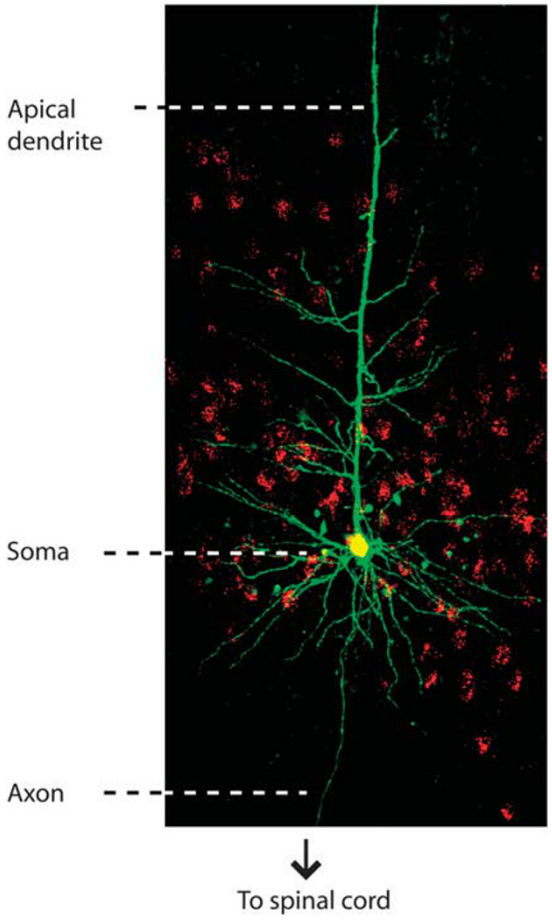

Figure 1. Corticospinal neurons in layer 5B of mouse motor cortex. Neurons were retrogradely labeled *in vivo* by injecting red fluorescent microspheres into the cervical spinal cord. Brain slices containing motor cortex were prepared, and a single corticospinal neuron was targeted for whole-cell patch recording with biocytin in the pipette solution. The slice was fixed and processed with streptavidin-conjugated green fluorescent dye for visualizing dendritic morphology. Red and green fluorescence images were acquired by 2-photon microscopy, and merged for display. Image provided by L Trapp and B Suter.