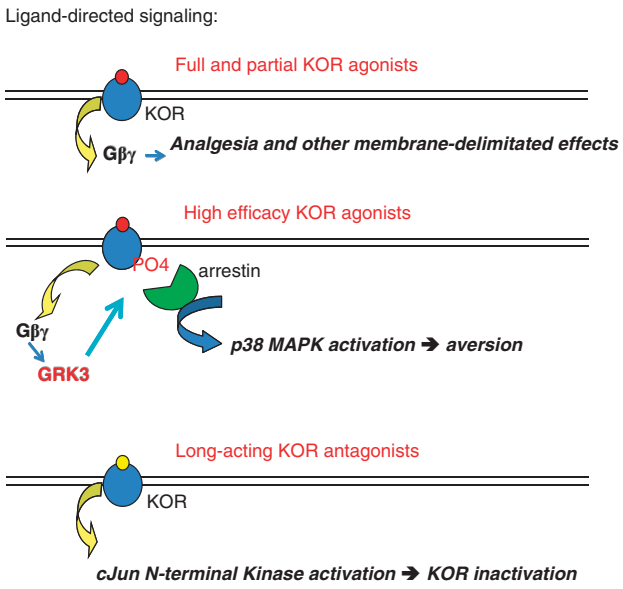

Figure 1. Three possible forms of ligand-directed signaling are illustrated.

2008). Consistent with the dysphoric effects of κ-agonist drugs and natural κ-opioids isolated from the plant *Salvia divinorum*, endogenous dynorphins encode a component of the anxiogenic and dysphoric responses to stressful experience.

Thus, κ-opioid antagonists show promise as therapeutic tools to promote stress resilience that may be effective in treating certain forms of anxiety, depression, and addiction disorders, as stress-hypersensitivity exacerbates each of these syndromes. However, selective κ-opioid antagonists have been known since their initial development by Portoghese and Takemori more than 20 years ago to have remarkably long durations of action. Although this property might be considered a therapeutic advantage (as infrequent dosing may be sufficient and missed doses would be less concerning), the lack of understanding of its basis has slowed drug development. We recently reported (Bruchas *et al*, 2007; Melief *et al*, 2010) that the long action was not a result of κ-receptor downregulation or drug persistence, but rather that these ligands were not truly competitive antagonists; instead their effects were caused by the activation of c-Jun N-terminal kinase (JNK) following κ-receptor binding (Figure 1). We think that JNK activation phosphorylates a component of the κ-receptor signaling complex, thus preventing G-protein activation and causing long-lasting receptor inactivation. This mechanism predicts that low-efficacy ligands that bind to κ-receptors without activating JNK may be short-acting antagonists. Conventional, competitive κ-antagonists may more easily gain approval.

The therapeutic promise of κ-agonists has also been recently revived by studies showing that their dysphoric effects require activation of G-protein receptor kinase, arrestin recruitment and subsequent p38 MAPK activation, whereas their analgesic effects do not (Bruchas and Chavkin, 2010). As evident from ligands initiating μ-opioid signaling, some analgesic opioids including fentanyl effectively recruit arrestin, whereas morphine is an excellent analgesic, but does not recruit arrestin. The realization that different agonists binding to the same receptor can produce different actions has been variously called 'biased agonism', 'functional selectivity', and 'ligand directed signaling' (see Melief *et al*, 2010). On the basis of this concept, an analgesic κ-opioid that did not recruit arrestin might not produce dysphoria (Figure 1). A formulation of such a ligand, combined with a peripherally restricted κ-antagonist to block the constipating and diuretic effects, might result in the long-sought non-addictive opioid analgesic. These are exciting times in the κ-world.

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New Treatments in Amyotrophic Lateral Sclerosis

Identification of New ALS Relevant Genes and Animal Model Development

For the past 15 years, the field of amyotrophic lateral sclerosis (ALS) pathophysiology and drug development has largely been dominated by

understanding the biology surrounding mutations in superoxide dismutase; the first gene mutation identified in familial ALS. In spite of a large amount of research surrounding the pathobiology of this mutation in animal models and *in vitro*, no successful human therapy has resulted from the many positive preclinical observations and clinical experiments based on mutant superoxide dismutase 1 (SOD1). The identification of two new familial ALS mutations in the past 2 years has potentially dramatically changed that. The identification of the TAR DNA-binding protein (TDP-43) in ubiquitinated protein aggregates found in many patients with sporadic ALS (but not familial SOD1-mediated ALS) or the most common form of frontotemporal dementia called frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U) has raised the possibility that this protein may be either a byproduct or an initiator of sporadic ALS (Lagier-Tourenne *et al*, 2010). The importance of this purely pathological observation was solidified and intensified when dominant mutations of TDP-43 were found in multiple ALS families and may account for up to 3% of familial ALS cases (Lagier-Tourenne *et al*, 2010). Perhaps equally significant has been the observation that almost all sporadic ALS post-mortem specimens have TDP-43 aggregates present in neurons and glia. Subsequently mutations in the RNA-metabolizing protein FUS were also found in a small subset of familial ALS patients. Thus, a new mechanism of familial ALS pathophysiology, aberrant RNA metabolism, suggested in sporadic ALS a decade earlier (Lin *et al*, 1998), appears to be an important ALS initiator. Importantly for the investigation of motor neuron disease, animal models using TDP-43 mutations have been developed, which afford a new model for the study of potential ALS-related drug therapies (Wegorzewska *et al*, 2009).

Biomarkers

ALS largely remains a clinical diagnosis based on the presence of upper and lower motor neuron signs that can be observed on physical examination and supported by electrophysiological studies and exclusion of other etiologies using serological and imaging studies. Current efforts are underway with both large consortia and individual groups to identify biomarkers from tissue or fluids that can establish the diagnosis early in the course of disease as well as an assessment of disease progression, identification of ALS subtypes, prediction of disease prognosis, and assessment of the therapeutic efficacy of drug candidates.

ALS Therapeutics: Small Molecules and Antisense Technologies

Recent advances in the identification of specific genes, which can cause ALS, have fueled the speculation that ALS may be a disease amenable to gene silencing technologies. For the most common ALS disease related gene (*SOD1*), both RNAi and antisense technologies have been used in transgenic mutant SOD1 animal models of ALS to show effective reduction of the SOD1 protein (Miller *et al*, 2005). A phase 1 safety trial using the CSF delivery of antisense oligonucleotides targeting SOD1 is now underway in patients with SOD1-mediated ALS (www.clinicaltrials.gov).

Cellular Therapy/IPS Cells

Perhaps the most important breakthrough in stem cell biology and its applicability to human diseases has been the ability to reprogram somatic cells into induced pluripotent stem cells (iPSC) using forced expression of the transcription factors Klf-4, Sox-2, Oct-4, and c-Myc, first in rodent, and then from human skin fibroblasts (Yu *et al*, 2007). Current efforts are underway from different investigators to create iPSC-derived neural stem cells from ALS patients. These iPSCs can subsequently be differentiated into multiple nervous system subtypes to aid in the understanding of cell-specific contributions to the development of ALS, screening for potential neuroprotective and neuroregenerating compounds, and potentially for their therapeutic potential in cell transplantation. The ability of specific CNS cells, such as astroglia, to alter ALS outcomes has been recently shown preclinically (Lepore, 2008). In parallel, the first commercial attempt to develop cellular-based therapies for ALS has entered into clinical trial. The proper cell for therapy is controversial and efforts, to date, appear to lack rigorous preclinical/drug discovery science. However, the first challenge in this invasive-type therapy is the development of appropriate surgical methods to deliver cells intraspinally to patients—and excellent efforts toward that goal appear underway in a recent phase 1 trial (www.clincialtrials.gov).

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DISCLOSURE

Dr Rothstein received compensation for serving as a scientific advisor to Cytokinetics, Pysadon Pharmaceuticals, Repligen, for clinical and/or preclinical drug discovery programs. He also serves as a grant reviewer for Muscular Dystrophy Association, National Institute of Health, Robert Packard Center for ALS Research at Johns Hopkins. Dr Maragakis serves as a grant reviewer for the US Department of Defense. He is a nonpaid scientific consultant to Q Therapeutics Inc.

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fMRI Studies of Reward Processing in Adolescent Depression

Reward function is increasingly considered to be an important aspect of affective disorders such as depression and bipolar disorder. Conceptual models of affective disorders emphasize disrupted reward function as a neural characteristic of low positive affect in depression, and studies with adults have indicated that brain function in reward-related regions distinguishes those with depression from healthy controls. Based on an interest in adolescence, as both a vulnerable period for the onset of affective disorders and a period of ongoing development of neural reward circuitry, an emerging literature is now addressing reward-related brain function in adolescents with depression. Results have generally paralleled those from adult studies and have indicated value in studying reward function in relation to the etiology, pathophysiology, and treatment of depression in young people.

Functional neuroimaging findings indicate that adolescents with depression (Forbes *et al*, 2009) and adolescents at risk for depression (eg, Gotlib *et al*, 2010) exhibit low striatal response to rewarding stimuli, such as money or happy facial expressions. This altered brain function has been observed during the anticipation of reward and the receipt of reward, suggesting that adolescent depression involves changes in both the motivation to obtain reward and the enjoyment of rewards once obtained.

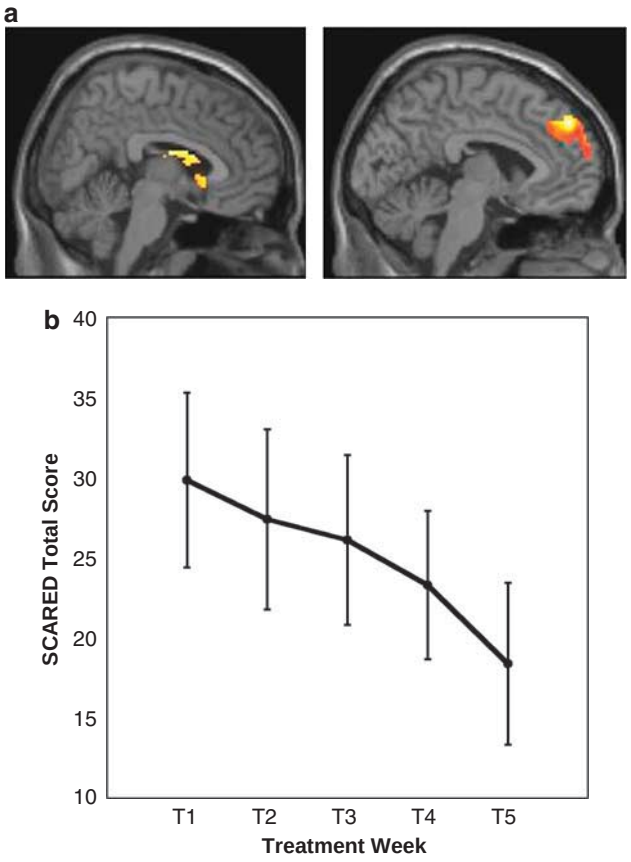

Figure 1. In adolescents with major depressive disorder, (a) response to reward anticipation in the striatum (left) and medial prefrontal cortex (right) at treatment entry was related to (b) rate of reduction in anxiety symptoms during an 8-week treatment with either cognitive-behavioral therapy or cognitive-behavioral therapy plus pharmacotherapy using selective serotonin reuptake inhibitors. Faster rate of decline in anxiety symptoms was predicted by greater striatal reactivity and lower medial prefrontal reactivity before treatment. Error bars represent 1SE of the mean at each time point. SCARED, Screen for Childhood Anxiety and Related Disorders (anxiety symptom measure); T1, pre-treatment; T2, treatment session 2; T3, treatment session 4; T4, treatment session 6; T5, treatment session 8 (post-treatment). The figure is based on the data published in Forbes *et al* (2010a).

In addition, there is also some evidence that adolescents with depression exhibit more reactivity in prefrontal regions thought to have a role in regulating response to reward stimuli. Consistent with the findings of increased anterior cingulate response to reward in adults with depression, adolescents with depression exhibit less response in the medial prefrontal cortex (PFC) (Forbes *et al*, 2009), an area that is a key target, along with the striatum, of midbrain dopamine neurons. The medial PFC is a critical region in reward circuits, and its efferent connections include the ventral striatum (Haber and Knutson, 2010).

The study of reward function has potential to elucidate many processes in the development and course of adolescent depression. Developmental findings that reward function changes with puberty and is associated with depressive symptoms in healthy adolescents (Forbes *et al*, 2010b) can inform the etiology of adolescent depression. Although the treatment implications of reward function research remain to be explored, initial findings suggest that adolescents' neural response to reward predicts symptom level and severity at outcome, as well as rate of symptom decrease during treatment for depression (Forbes *et al*, 2010a; Figure 1).