morphometric measures are available, but have not been firmly established as markers for these purposes. Markers that can be detected in easily obtainable biofluids would be ideal for these purposes and would increase the power to detect the effect of therapeutic agents in a shorter time with reduced cost.

Unbiased exploratory examination of panels of RNAs, both mRNA and noncoding RNAs, exosomes, proteins, antibodies, and metabolites in small individual cohorts have yielded promising candidate markers that yearn for replication in independent cohorts (Kroksveen *et al*., 2011). More targeted approaches to identify biomarkers based on PD pathophysiology have shown disease-related proteins as strong candidates. Alpha-synuclein is decreased in the cerebrospinal fluid of PD patients (Hong *et al*., 2010), although significant overlap with controls makes it less useful in assisting individual diagnosis. Other potential protein candidates include DJ-1 and inflammatory cytokines. Post-translationally modified forms of these proteins may improve the biomarker specificity. Most of these studies have utilized CSF (Parnetti *et al*., 2013), although increased oxidized DJ-1 in PD patients was detected in blood (Saito *et al*., 2009) and epidermal growth factor levels in plasma has been shown to predict cognitive decline in PD (Chen-Plotkin *et al*., 2011). Ultimately one could predict that a panel of multiple biochemical markers could be combined to increase the accuracy of diagnosis and disease progression. Heterogeneity of patient populations and lack of standardization of collection methods may contribute to the inconsistent and variable observations in the literature.

A major need in the field is the availability of biospecimens from well-characterized cohorts for discovery of new biomarkers and validation. In response to these needs, three major programs have been launched. The Parkinson's Progression Marker Initiative (PPMI) is a prospective study of 400 newly diagnosed PD patients and 200 controls that will be followed over 5 years and collect extensive clinical (motor and non-motor information), imaging, and biosample (blood, cerebrospinal fluid, DNA/RNA from blood, urine) information from all 600 subjects at sites around the world (Marek, 2011). PPMI expanded to include a prodromal cohort of 100 individuals at risk for developing PD to develop biomarkers that are present prior to the onset of clinical motor symptoms. The Fox Investigation for New Discovery of Biomarkers (BioFIND) is a study supported in collaboration with National Institute of Neurological Diseases and Stroke (NINDS) focused on novel biomarker discovery by enrolling 120 rigorously defined clinically typical PD in mid-stage and 120 age- and gender-matched controls at one timepoint in US sites. BioFIND was launched to serve as a platform to test new biomarkers in somewhat narrow spectrum of clinically typical PD in moderate stages to maximize the chance of discovering differences in a less heterogeneous population. The Parkinson's Disease Biomarker Program (PDBP) is a program designed to support new and existing biomarker cohorts that collect biospecimens using standardized protocols. Biospecimens and data from all above studies are available to the research community. Through standardization and coordination of data and sample collection, we are optimistic that new markers will emerge which will assist in clinical trials and ultimately result in improved management of the disease.

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Neurotherapeutic Implications of Brain-Immune Interactions

Results suggest a cause and effect relationship between inflammatory cytokines and symptoms relevant to a number of psychiatric illnesses including mood and anxiety disorders, as well as schizophrenia. In addition, data indicate that immune cells may have a critical role in neuronal integrity and the prevention of developmental diseases including Autism Spectrum Disorders (ASD). These findings highlight the nuanced role of the immune system in brain health and illness, and emphasize the exciting potential of neurotherapeutics that target the immune system to treat neuropsychiatric disorders.

A recent clinical trial was conducted to determine whether antagonism of the inflammatory cytokine tumor necrosis factor (TNF) would reduce depressive symptoms in patients with treatment resistant depression (TRD), thereby testing the cytokine hypothesis of depression (Raison *et al*, 2013). Interestingly, only TRD patients with a baseline peripheral blood concentration of C-reactive protein (CRP—a readily available biomarker of inflammation) >5 mg/l exhibited a clinically significant response to infliximab

compared with placebo, indicating that within TRD patients, there appears to be a subgroup of individuals whose depressive symptoms are driven by TNF-induced inflammation in a cause and effective manner. Plasma concentrations of TNF and its soluble receptors as well as peripheral blood expression of TNF-regulated genes also discriminated infliximab responders vs nonresponders as did genes that regulate gluconeogenesis and lipid metabolism, suggesting an interaction between inflammatory pathways and pathways related to the metabolic syndrome in predicting response to cytokine antagonism (Figure 1) (Mehta *et al*, 2013). Symptom dimensions that improved in infliximab vs placebo-treated patients with CRP >5 mg/l included anhedonia, psychomotor retardation, and anxiety. These behaviors are common to multiple psychiatric illnesses and are thought to be mediated by specific brain regions, such as the basal ganglia and dorsal anterior cingulate cortex, which are targets of inflammatory cytokines (Miller *et al*, 2013). These findings suggest that cytokines may have specific effects on symptoms domains across disorders, and that relevant patients for immune-targeted therapies can be identified by plasma inflammatory biomarkers or gene expression profiles related to inflammation and the metabolic syndrome.

Regarding the participation of the immune system in neuronal integrity, data has indicated that T cells have a fundamental role in learning and memory as well as neurogenesis. For example, T-cell deficient mice perform poorly in multiple cognitive tasks, including the Morris water maze, and exhibit impaired neurogenesis in an enriched environment (Ziv *et al*, 2006). The mechanisms of these effects appear to be related to the ability of T cells to produce IL-4, which stimulates the release of growth factors from astrocytes, and promotes the conversion of microglia and macrophages from an inflammatory M1 phenotype to a neuroprotective M2 phenotype (Derecki *et al*, 2010). Complementing these data are recent findings that transplantation of wild-type microglia into a genetically induced mouse model of Rhett's syndrome markedly attenuated disease development including impaired open-field behavior and rotarod performance, decreased body weight, and reduced lifespan. (Derecki *et al*, 2012). In most cases, Rhett's syndrome, an ASD, is the result of a mutation of the *MECP2* gene that encodes a methyl-CpG-binding protein that is expressed in multiple cell types including neurons, where in mutated form, it leads to neuronal dysfunction. The mutated *MECP2* gene is also expressed in glial cells including microglia. Interestingly, transplantation of wild-type microglia (lacking the mutated *MECP2* gene) markedly reduced disease expression, indicating the importance of microglia in neuronal integrity and disease development in ASD.

Taken together, these data highlight the multiplicity of roles played by the immune system in neuropsychiatric disorders, and indicate that managing immune responses represents a new era in neuropsychopharmacology and immunology.

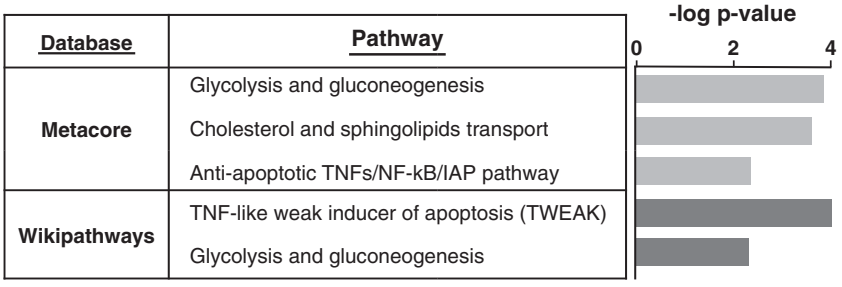

Figure 1. Gene expression pathways that significantly predicted antidepressant response to infliximab. Genes at baseline that were significantly predictive of infliximab treatment response (50% reduction in 17-item Hamilton Depression Rating Scale at any point during the study; $n=148$, 1.2-fold change, $P\leqslant 0.01$) were involved in pathways related to glycolysis and gluconeogenesis, cholesterol and sphingolipid transport, and apoptosis through tumor necrosis factor (TNF)-related signaling pathway as assessed using Metacore and Wikipathways. Reprinted from Mehta *et al*, 2013, with permission from Elsevier.

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