laboratory, a subsequent PET scan showed reduced [^{11}C] GR103545 binding compared to CUD subjects' baseline scans. This reduction in radioligand binding suggests that increased endogenous dynorphin is competing for KOR-binding sites and supports the prior animal literature showing that binge cocaine use modifies this neurotransmitter system. Together, these findings support the negative affect state hypothesis of addiction and implicate that the dynorphin–KOR system is a central part of this state in humans with CUD.

Prior to our combined human laboratory and PET imaging study, there was a limited understanding of the potential clinical role for KOR antagonists in CUD. A multi-site placebo-controlled trial of combined buprenorphine (a potent kappa antagonist and partial mu agonist) and extended-release naltrexone (a non-specific opioid receptor antagonist) showed mixed results [5], although this may have been affected by the mu receptor activity of naltrexone. More recently, a selective KOR antagonist LY2456302 was shown to be well-tolerated in CUD patients, showing feasibility for future clinical trials [6].

The confluence of data in animal models, post-mortem human studies, and now human PET imaging robustly supports the need for clinical studies of KOR antagonists that focus on stress-induced relapse. Future success with KOR antagonists will depend on targeting the "dark side" of addiction, by selectively recruiting participants who relapse in the setting of stress and dysphoria.

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The authors declare no competing interests.

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Targeting neuroinflammation with brain penetrant P2X7 antagonists as novel therapeutics for neuropsychiatric disorders

Anindya Bhattacharya[1] and Marc Ceusters[2]

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Several lines of scientific data suggest a correlation between neuroinflammation and CNS disorders such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy, chronic pain and neuropsychiatric disorders (depression, bipolar disorder and schizophrenia). Many of these CNS diseases are comorbid with classical peripheral inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, to name a few. The scientific underpinning of this comorbidity in patients is perhaps driven by a compromised immune surveillance system wherein the immune cells and cytokines/chemokines in the periphery cross-talk to the CNS either directly (BBB integrity compromise) or indirectly via modulating meningeal immunity. In addition, there is an inherent '*central*' component of neuroinflammation that is driven by microglial cells within the CNS. As such, neuroinflammatory drug targets on microglia cells within the CNS have been an emerging area of research within the neuroscience community, both in academia, industry and in public-private consortia.

P2X7 is an ATP activated ion channel, that is expressed abundantly on microglia (and peripheral immune cells) and is a critical mediator of neuroinflammation via release of NLRP3 dependent IL-1β and IL-18 [1]. In several preclinical models of stress in rodents, independent research groups have demonstrated an activated NLRP3-IL1β pathway; as such intervention of this pro-inflammatory pathway by targeting the P2X7 ion channel with CNS penetrant antagonists have demonstrated efficacy in models of psychiatric diseases [2] and provides optimism for novel therapeutic options for patients with mood disorders. When ATP is present in high concentrations in extracellular space as a danger signal, the P2X7-NLRP3- IL1β signaling is activated initiating the microglial neuroinflammatory cascade. The functional expression of this pathway may or may not be associated with enhanced expression of P2X7 at the protein level

[1]Neuroscience Therapeutic Area, Janssen R&D LLC., 3210 Merryfield Row, San Diego, CA 92121, USA and [2]Neuroscience Therapeutic Area, Janssen R&D LLC., Turnhoutseweg 30, Beerse 2340, Belgium
Correspondence: Anindya Bhattacharya (abhatta2@its.jnj.com)

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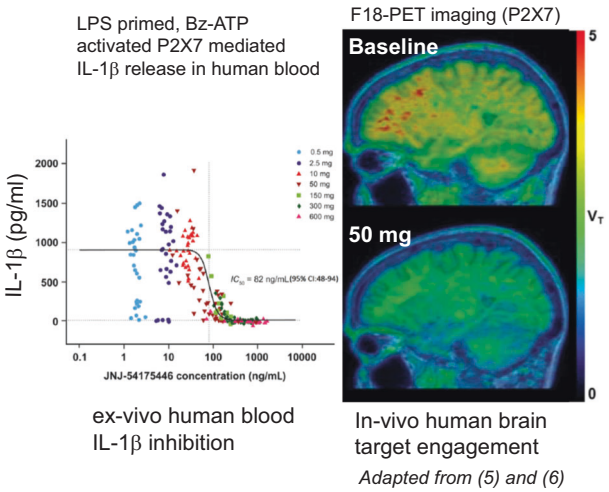

Fig. 1 Incremental human plasma exposure of the P2X7 antagonist JNJ-54175446 caused a dose dependent attenuation of P2X7 dependent ex-vivo IL-1β release (ex-vivo LPS primed, ex-vivo Bz-ATP as 2nd stimulus) from human subjects (left). The dose of 50 mg JNJ-54175446 produced central target engagement as assessed by displacing the P2X7 PET ligand, [^{18}F]JNJ-64413739 (right)

and an absence of P2X7 upregulation should not be taken as proof of absence of P2X7 in the disease process. Patients with inflammatory burden and activated immune cells with enhanced IL-1β and IL-18 signaling, ought to be tested in controlled clinical studies with doses of P2X7 antagonists that satisfy target engagement of brain P2X7 channels in humans.

We have recently disclosed two brain penetrant P2X7 antagonists in JNJ-54175446 [3] and JNJ-55308942 [4]. In a phase I single ascending dose study in human subjects, JNJ-54175446 demonstrated dose dependent increases in plasma exposure, CSF exposure and ex-vivo inhibition of IL-1β from human blood (Fig. 1) [5]; more importantly, the P2X7 antagonist demonstrated robust occupancy at the human brain P2X7 as was assessed by a PET study (Fig. 1) [6]. Preliminary data from two Phase 1 human experimental medicine studies indicates a central effect of JNJ-54175446 in sleep deprived and amphetamine challenged human subjects (ACNP 2018) setting the stage for proof of concept testing in treatment resistant depression (http://www.isrctn.com/ISRCTN44411633). We remain optimistic based on the preclinical body of evidence that P2X7 antagonism will bring in novel therapeutic options for patients and their physicians, either as mono/adjunctive therapies to address the unmet need in neuropsychiatry.

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Biological fingerprints for psychosis

Carol A. Tamminga[1] and Brett A. Clementz[2]

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It is generally acknowledged that once the nosology of psychiatric disorders finds a basis in neurobiology, the field will be more successful at specifying, finding treatments, and predicting outcomes for psychiatric conditions.

THE NEED FOR BIOLOGY-BASED PARSING IN PSYCHOSIS

Leaders in psychiatry have called for biologic characteristics to be the basis for designating psychiatric diagnostic groups. Most recent efforts have focused on genetics for biological classification, despite the weak genetic effects for the psychoses [1]. Geneticists themselves have concluded that their results "strongly suggest that our diagnostic categories do not define pathophysiological entities" [2]. Therefore, seeking clues to biology, we have turned to a comprehensive characterization of quantitative behavioral, cognitive, electro-physiologic, and imaging traits (each with some but not complete biological understanding) in a cross-diagnostic psychosis population.

[1]Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA and [2]Departments of Psychology and Neuroscience, University of Georgia, Athens, TX, Georgia
Correspondence: Carol A. Tamminga (Carol.tamminga@utsouthwestern.edu)

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