Reverse and Forward Translational Neuropharmacology in Psychiatric Drug Discovery

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The probability of achieving marketing approval of a novel therapeutic for psychiatric indications is extremely low due largely to the inability to demonstrate durable and reproducible efficacy in phase II trials and beyond. These failures are often attributed to the lack of translation of the underlying neuropharmacology from animal model(s) to the disease population. However, how assured is such a conclusion considering the clinical efficacy path rarely meticulously parallels the preclinical experiment(s) that underwrote it?

**OVERVIEW**

In drug discovery and early clinical development, translational pharmacology occurs when the same drug-dependent effect is observed preclinically and clinically at a targeted drug exposure. Such translatability encompasses biomarker and efficacy measures as well as safety/tolerability, particularly for mechanism-mediated adverse events (AEs). Importantly, however, are the numerous variables underlying “translational pharmacology” that must be carefully assessed to determine if it is indeed achieved, such as: interspecies differences in target expression and/or drug potency; concordance between animal model(s) and the tested clinical population; an identical or essentially equivalent biomarker and/or behavior; and the temporal exposure–response relationship in the preclinical model vs. that tested in humans (e.g., acute vs. chronic dosing, direct vs. indirect pharmacokinetic-pharmacodynamic relationship), which ultimately dictates the optimal dosing regimen(s) for translational pharmacology studies. These analyses require the systematic integration of highly interdisciplinary data with seamless nonclinical and clinical interactions, especially for therapeutic indications lacking a clinical gold standard to enable high-confidence reverse translation.

In addition to these considerations, translational neuropharmacology is uniquely challenged by the requirement of a systemically dosed therapeutic to cross the blood–brain barrier satisfactorily, which is sometimes very different across species. It may be argued that many “negative” neuroscience clinical trials were unsuccessful due more to inadequate central drug exposure for full neuropharmacological evaluation than to a conceptually flawed mechanistic rationale or truly absent translational pharmacology. Fortunately, significant advances in more fully understanding and manipulating test-molecule neuropharmacokinetics to optimize central target engagement, and an adaptation to diligently establishing quantitative exposure–target engagement–biomarker effect relationships before initiating larger proof-of-concept trials, should allow confidently vetting future neuropharmacological mechanisms.

Successful reverse translation is so critical not only to allow preclinical studies to better understand the underlying neuropharmacology, but to enable the testing of other mechanisms that may undergo forward translation for their own clinical evaluation; together, such directional translations comprise an iterative approach. An example of an ideal psychiatry-centric reverse translational pharmacology correlation is with selective serotonin reuptake inhibitors, where 80% serotonin transporter occupancy affords antidepressant efficacy.1 This clinically established target occupancy-based outcome biomarker has been backtranslated to preclinical models for further research. Another seemingly effective neuropharmacological reverse translation is for L-DOPA-induced dyskinesia in Parkinson’s disease (PD-LID) via the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-rendered Parkinsonian nonhuman primate model (MPTP-NHP), in which PD-LID-tested metabotropic glutamate receptor 5 negative allosteric modulators suggest a receptor occupancy of ≥80% is required for efficacy in both MPTP-NHP and PD-LID. As these examples accentuate, such associations require not only extensive clinical datasets, but a clinically validated imaging agent to quantitatively link drug concentration to target engagement and it to clinical outcome. Therefore, the confident assessment of the translation of neuropharmacological mechanisms requires the careful, and often iterative, approach of matching across species the precise temporal exposure–response relationship, which is ideally linked quantitatively

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to drug–target engagement (i.e., occupancy). Unfortunately, one often lacks the ability to directly establish such target-occupancy relationships, which makes assured reverse translation more difficult, particularly for molecules with polypharmacology.

A recent highly encouraging example of reverse translation in psychiatry is with ketamine, an anesthetic discovered in the 1960s. As summarized herein, the bridging of ketamine’s clinically observed cognitive impairment (an AE) and antidepressant efficacy at consistent interspecies exposures has facilitated mechanistic studies and new drug evaluation for both cognitive impairment associated with schizophrenia (CIAS) and major depressive disorder (MDD). Furthermore, application of a backtranslated ketamine-induced cognitive impairment NHP model to clinically translate a novel mechanism proposed for CIAS is illustrated to highlight opportunities to enhance psychiatric translational neuropharmacology.

KETAMINE: REVERSE TRANSLATION

Ketamine is a nonselective N-methyl-D-aspartate receptor (NMDAR) antagonist. For years, ketamine has been of great interest in psychiatry because its acute administration to healthy volunteers (HV) at lower, nonanesthetic doses generates transient schizophrenia-like psychosis and cognitive impairment, further supporting the hypothesis that NMDAR hypofunction and/or glutamatergic dysregulation underlies schizophrenia pathophysiology. Via dose (not exposure)–response behavioral studies in rats and NHP, neuropharmacologists backtranslated these clinically observed ketamine effects to develop experimental animal models in which novel molecules could be evaluated for their antipsychotic and/or procognitive properties. Although such models were developed fairly successfully, only recently was a careful exposure–response evaluation performed for ketamine’s cognitive-impairing doses in rats, NHP, and humans using predicted NMDAR occupancy (RO) as the common anchor. Interestingly, the analysis found that essentially the same degree of RO that caused cognitive impairment in humans did the same in an NHP model of spatial working memory (Figures 1, 2); at the RO that elicits psychotomimetic effects in humans, NHP also experienced temporary positive- and negative-like symptoms. In rats, ketamine-induced cognitive deficits occurred at higher or equivalent clinically relevant RO depending on the utilized rat model. Thus, based on the successful backtranslation of ketamine’s cognitive-impairing effects in humans to NHP and rat spatial working memory assays and the NMDAR-related hypothesis for schizophrenia, researchers have used these models to determine nootropic exposures of experimental drugs for CIAS-related testing. Yet a clinical evaluation of the forward translational value of these preclinical ketamine-disrupted models has only just occurred (see below).

There is also considerable excitement in psychiatry attributable to the highly reproducible efficacy of ketamine in MDD patients. However, there is great debate as to the precise mechanism(s) underlying ketamine’s antidepressant profile, which seems to be an indirect effect, unlike its untoward properties that are direct effects. By using the aforementioned RO-normalization methodology at the clinical antidepressant dose, an infusion paradigm has been projected for rats that mirrors the clinically relevant exposure–RO–time relationship. Applying this dosing regimen, or ones closely paralleling it, researchers may use rat models to optimally investigate the underlying mechanism(s) of ketamine’s antidepressant effects. Identifying the mechanistic pathway(s) should provide greater insights into which pharmacological target(s) to best engage to potentially simultaneously elicit ketamine’s desired efficacy without its AEs.

AMPA POTENTIATOR: FORWARD TRANSLATION

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) mediate fast glutamatergic excitatory neurotransmission
whose activation increases NMDAR-mediated changes in the synaptic and morphological function thought to underlie learning and memory. Thus, AMPAR potentiation is predicted to be effective at treating CIAS since it is believed to primarily result from dysfunction in NMDAR glutamatergic neurotransmission. This theory is supported by studies with ketamine in HV, whose memory deficits have been backtranslated to preclinical models as described earlier. Using rat and NHP (Figure 2) models of pharmacologically induced NMDAR hypofunction, a series of evaluated AMPAR potentiators afforded clinical candidate PF-04958242 that reduced ketamine-mediated working memory impairments at an interspecies-consistent mean unbound brain drug concentration (\(C_{\text{hu}}\)) of 0.3 nM, which equated to a human total plasma drug concentration of 2.4 ng/mL.2

After establishing safety, tolerability, and pharmacokinetics in HV, PF-04958242 was evaluated for its ability to attenuate ketamine-induced impairment in verbal learning and memory.5 Most important, from a forward-translation perspective, ketamine and PF-04958242 dosing regimens were strategically selected to parallel the precise temporal exposure–response for both drugs defined in NHP spatial working memory studies (Figure 1). Specifically, PF-04958242 was dosed to steady-state to afford PF-04958242 \(C_{\text{hu}}\) of ~0.3 nM at the time of cognitive evaluation to perfectly parallel that performed in the nonclinical models. The employed (and previously reverse-translated) ketamine infusion had clinical precedence for safely generating an array of effects relevant to schizophrenia, including verbal learning and memory deficits, transient psychosis-like effects, and perceptual alterations. The clinical study found that PF-04958242 significantly reduced ketamine-induced impairments in immediate recall (Hopkins Verbal Learning Test, \(P = 0.039\)) and two-back (\(P = 0.001\)) and spatial working memory (\(P = 0.006\)) tasks (CogState Battery), without significantly attenuating ketamine-dependent psychotomimetic effects. Exposure data for ketamine, norketamine (its 6-fold less-potent active metabolite), and PF-04958242 during the behavioral assessments showed that there were no pharmacokinetic interactions between any of these molecules, and the range of projected RO and PF-04958242 \(C_{\text{hu}}\) mirrored those observed to be effective in the rat and NHP (Figure 1) models. The observation that PF-04958242 tempered ketamine-induced cognitive deficits in humans at similar PF-04958242 concentrations and projected RO to those observed in ketamine impairment assays in both rat and NHP models strongly suggests a translatable pharmacokinetic-pharmacodynamic effect for this mechanistic interaction. This translational neuropharmacology study helped substantiate progressing PF-04958242 to a CIAS proof-of-concept trial.

Although such excellent interspecies agreement is rarely demonstrated in psychiatric drug development, this example clearly highlights the meticulous correlation of preclinical and clinical study parameters to optimize the chance of determining the true translational neuropharmacology of a particular mechanism for a particular clinical endpoint.

CONCLUSION

As exemplified by ketamine, the iterative loop of translational pharmacology typically demands focused attention over significant time. With the increased emphasis and advances in establishing ever-prompter in drug discovery and early clinical development the temporal central exposure-target engagement-biomarker-behavioral relationship in animal models and humans, the field of neuropharmacology will be better informed as to what mechanisms warrant further clinical development while better understanding which biomarkers are truly linked to clinical outcomes. It is highly likely that not all neuropharmacology will directly translate between the preclinical and clinical realms, but determining translatability unequivocally will be best enabled by applying the discussed concepts. Research institutions must be patient with the intrinsically demanding cycles of translational neuropharmacology to optimize their chances to identify transformative therapies for psychiatric diseases.

CONFLICT OF INTEREST

C.L.S. is a full-time employee of Pfizer Inc. and owns, and/or holds options and/or restricted stock units for, the company’s publicly traded shares.

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