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Review

REVIEW

Strategies for Utilizing Neuroimaging Biomarkers in CNS Drug Discovery and Development: CINP/JSNP Working Group Report

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Abstract

Despite large unmet medical needs in the field for several decades, CNS drug discovery and development has been largely unsuccessful. Biomarkers, particularly those utilizing neuroimaging, have played important roles in aiding CNS drug development, including dosing determination of investigational new drugs (INDs). A recent working group was organized jointly by CINP and Japanese Society of Neuropsychopharmacology (JSNP) to discuss the utility of biomarkers as tools to overcome issues of CNS drug development.

The consensus statement from the working group aimed at creating more nuanced criteria for employing biomarkers as tools to overcome issues surrounding CNS drug development. To accomplish this, a reverse engineering approach was adopted, in which criteria for the utilization of biomarkers were created in response to current challenges in the processes of

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drug discovery and development for CNS disorders. Based on this analysis, we propose a new paradigm containing 5 distinct tiers to further clarify the use of biomarkers and establish new strategies for decision-making in the context of CNS drug development. Specifically, we discuss more rational ways to incorporate biomarker data to determine optimal dosing for INDs with novel mechanisms and targets, and propose additional categorization criteria to further the use of biomarkers in patient stratification and clinical efficacy prediction. Finally, we propose validation and development of new neuroimaging biomarkers through public-private partnerships to further facilitate drug discovery and development for CNS disorders.

Keywords: CNS drug development, neuroimaging biomarkers, public-private-partnerships, patient stratification, clinical efficacy prediction

Significance Statement

Recent central nervous system (CNS) drug discovery and development has been largely unsuccessful. Biomarkers, particularly those utilizing neuroimaging, have played important roles in aiding CNS drug development, including dosing determination of investigational new drugs (INDs). The consensus statement from working group organized jointly by CINP and Japanese Society of Neuropsychopharmacology (JSNP) propose a new paradigm containing five distinct tiers to further clarify the use of biomarkers in patient stratification and clinical efficacy prediction and establish new strategies to develop new neuroimaging biomarkers through public-private-partnerships (PPPs) that combine disease knowledge, cutting-edge technologies, chemical libraries, medicinal chemistry and funding to achieve novel breakthroughs.

Introduction

Most current medications for psychiatric disorders stem from mechanistic optimizations of agents serendipitously discovered approximately 60 years ago. While these discoveries have led to the development of next generation drugs, including the antipsychotics and antidepressants widely prescribed today, much remains to be desired in this arena; although newer drugs show fewer serious side effects than first-generation compounds, many current medications are plagued by lingering safety and efficacy issues (Becker et al., 2015). In an effort to overcome these, current drug discovery strategies have, by necessity, evolved to focus on novel molecular targets that influence neural systems not previously targeted by legacy drugs.

Although symptom-improving drugs have been developed for several intractable CNS disorders (e.g., acetylcholinesterase inhibitors for Alzheimer's disease (AD)), current drug discovery efforts have shifted to the development of disease-modifying agents that interfere with the neurodegenerative processes that may underlie disorders whose etiologies are not fully understood (Becker et al., 2015).

However, despite the wide array of new drug targets, success rates in developing new CNS drugs have not increased for many years. Clinical trials of recently discovered agents frequently fail, mostly owing to a lack of efficacy (Griebel and Holsboer, 2012; Dunlop and Brandon, 2015). As a result, global pharmaceutical companies have ceased or reduced their efforts in this space.

To identify avenues to overcome these problems, the Collegium Internationale Neuro-Psychopharmacologicum (CINP) convened a summit meeting (CNS Drug Innovation Summit Meeting) in Tokyo in April, 2015 to discuss options for facilitating more efficacious drug discovery and clinical development activities for CNS disorders, activities ultimate aimed at increasing success rates in current and future clinical trials. Based on discussion during the meeting, 3 working groups including researchers in academia and industry were organized jointly by CINP and Japanese Society of Neuropsychopharmacology (JSNP) to put forth potential solutions. At the following meetings, 2 factors were noted as major barriers to improving success rate of CNS drug development.

(1) Difficulties in designing appropriate clinical plans for clinical proof-of-concept (POC) studies: To conduct successful clinical POC studies, appropriate setting of optimal dose(s) and patient stratification are critically important factors. Without control of these variables, one could not reasonably conclude that an on-target investigational new drug (IND) is ineffective or, worse, invalid. Moreover, both dosing and patient stratification should be determined based on the concept or mechanism the drug target stands on. While this is seemingly evident, methodologies to satisfy these issues have not been clearly established.

(2) Difficulties predicting clinical efficacy: Development of biomarkers, which can substitute for clinical endpoints, is increasingly critical for predicting clinical efficacy. Considering, however, the limited biomarkers currently available for most CNS disorders, it is often difficult to confidently predict clinical outcomes in small-scale efforts preceding larger, more expensive trials. As an implicit corollary, the lack of reliable and objective biomarkers is an additional hurdle for pharmaceutical companies engaging in challenging clinical POC studies.

It has become increasingly evident that continued development and implementation of biomarkers will closely follow successes in overcoming the above-mentioned barriers. In attempting to improve and accelerate this process, we first analyzed the current challenges to (and utilization of) biomarkers in the current drug discovery landscape (section 2) and used this as a starting point a newly proposed process for clinical POC studies based on real-world observation (section 3). Then we propose the development and validation of new biomarkers to achieve successful clinical POC studies through public-private partnerships (PPPs) (section 4). In this CINP/JSNP working group report, we focus heavily on neuroimaging biomarkers due to their widely acknowledged utility as a noninvasive tool in CNS disorders (Wong et al., 2009).

Roles of Neuroimaging Biomarkers in Drug Discovery and Development of CNS Disorders

Morgan et al. (2012) previously described a 3-pillar model for biomarker utilization in successful clinical development, consisting of the following: (1) drug exposure at the site of action for the

desired length of time; (2) drug binding to the intended target; (3) evidence of functional modulation of the target organ resulting from the drug pharmacological activity (for example pharmacological functional magnetic resonance imaging (phMRI), a method for analysis of the drug-induced functional changes in the neural circuits (Wandschneider et al., 2016). In their review, it was mentioned that a clinical development candidate that satisfies all 3 pillars will (1) have increased likelihood of surviving through Phase II into Phase III, and (2) enable efficient and effective development through POC and Phase II.

The current state of biomarker usage (taking into account the 3 pillars concept) in recently conducted clinical trials for CNS disorders is listed in Table 1. Several issues emerging from meta-analyses of these trials are discussed below.

Psychiatric Disorders

The 3-pillar concept has gained widespread acceptance across pharmaceutical companies. For example, measurement of drug levels in the cerebrospinal fluid (CSF) (Lin, 2008; Caruso et al., 2013) and occupancy of target molecules using positron emission tomography (PET) has become commonplace, particularly for well-investigated targets like the dopamine D2 receptor (for antipsychotics) (Farde et al., 1988; Kapur et al., 2000; Arakawa et al., 2008) and serotonin transporter (for antidepressants) (Meyer et al., 2001; Suhara et al., 2003). Thus, while the implementation of pillar 2 depends on the availability of a PET tracer, the strategy for measuring occupancy has been established and the importance widely acknowledged.

However, a number of INDs employing new mechanisms of action (ex: positive allosteric modulators) (Conn et al., 2014) loom on the horizon. For some agents with new mechanisms or modes of action, the relationship between drug efficacy and target occupancy has not been well established or remains unclear. Therefore, there is an increasing need for dose selection rationales based on changes in neuronal circuitry (i.e., pillar 3) to confirm that target occupancy relates to changes in neural function. As for any new approach, significant issues require addressing, including (1) the absence of consensus regarding methodology, (2) the absence of fully validated or standardized methods, and (3) variations in the definition of pillar 3, often owing to differing biomarker criteria that results in significant company-to-company variations in patient stratification, dosing, and efficacy endpoints.

In part because of these issues, we believe it is necessary to redefine the existing pillars to further clarify the use of biomarkers as well as to establish new strategies for decision-making in the context of CNS drug development.

Neurodegenerative Disorders

In the clinical development of disease modifiers for neurodegenerative diseases, AD in particular (Salloway et al., 2014; Siemers et al., 2016), there is no precedent for the application of biomarkers under pillar 2 (although use in enzyme inhibition mechanism like β-secretase inhibitors is theoretically possible) with biomarkers falling under pillar 3 being substituted to various ends. However, these parameters may be too broad to adequately categorize biomarkers with different and/or overlapping utilities.

To illustrate this point, consider the following: an amyloid-lowering strategy has long been the mainstream approach in AD-modifying drug development (Hardy and Selkoe, 2002; Golde, 2005; Tanzi, 2005). Amyloid PET imaging is a well-established method to investigate the accumulated amyloid in the brain (Klunk et al., 2004; Jagust et al., 2009; Clark et al., 2012), an approach that doubles as an effective screening tool for enrollment of appropriate patients into clinical trials. Recently, a small POC trial of an amyloid-targeting antibody showed promise as both a potential biomarker and therapeutic that offered cognitive benefits (Ratner, 2015; ALZFORUM). In the ensuing clinical trial, all of the enrolled subjects were confirmed amyloid positive by amyloid PET imaging. The concomitant use of brain imaging and fluidic biomarkers illustrates how pillar 3 biomarker may maintain dual roles in patient enrollment and efficacy prediction of targeted pharmacological action. As such, more detailed categorization of pillar 3 biomarkers into subclasses may be preferable for early and efficient decision-making during the drug development phase.

Redesign of Biomarker Classification to Improve the Success Rate of CNS Drugs

As discussed above, success rates of CNS drugs in clinical POC studies would almost certainly benefit from optimal dose selection, patient stratification, and efficacy prediction in a small-scale trial. Information derived from both target occupancy data and consequent functional change(s) in the brain can improve the accuracy of optimal dose selection to achieve maximal efficacy. Functional changes in the brain can be measured by multiple methods, including phMRI and electroencephalography (EEG); however, these methods can sometimes detect confounding and/or nonspecific reactions within the brain. Because of this, we propose to redefinition of pillar 3 to better clarify purpose.

Furthermore, while the 3 pillars paradigm remains a useful tool for estimating clinical success, a more precise use of biomarkers, including biomarkers for patient stratification and efficacy prediction, can further improve the success rates in CNS drugs development trials. In this report, we propose redesign and expansion of the existing classification system into one constituting 5 unique tiers relating to different aspects of biomarker utility (Figure 1a-b). In the proposed system, the increased specificity of additional tiers allows for improved estimation of drug action (and subsequent systemic reaction), resulting in an increasingly descriptive toolkit for ensuing clinical POC studies.

Tier 1: Brain Exposure over the Application Period

Sufficient drug exposure is a prerequisite for drug action; however, accurate measurement of CNS drug exposure to target sites in the brain can be quite challenging. The majority of CNS drugs penetrate into brain via blood circulation; thus, PK/PD modeling using plasma exposure has been afforded a certain level of significance. Similarly, microdosing of labeled drugs and intracerebral microdialysis of CSF or interstitial fluid have also been employed in assessing drug pharmacokinetics (Lin, 2008; Burt et al., 2016).

However, it should be noted that these methods have certain limitations; blood PK/PD modeling cannot infallibly predict precise CNS exposure of a given drug, and microdosing of a labeled drug does not measure its free fraction. In addition, there are ethical issues attached to sampling interstitial fluid from healthy volunteers, and CSF drug concentration can differ significantly from those at target brain regions due to route of administration and variance arising from circulation within the ventricular compartment.

Tier 2: Target Engagement Biomarkers

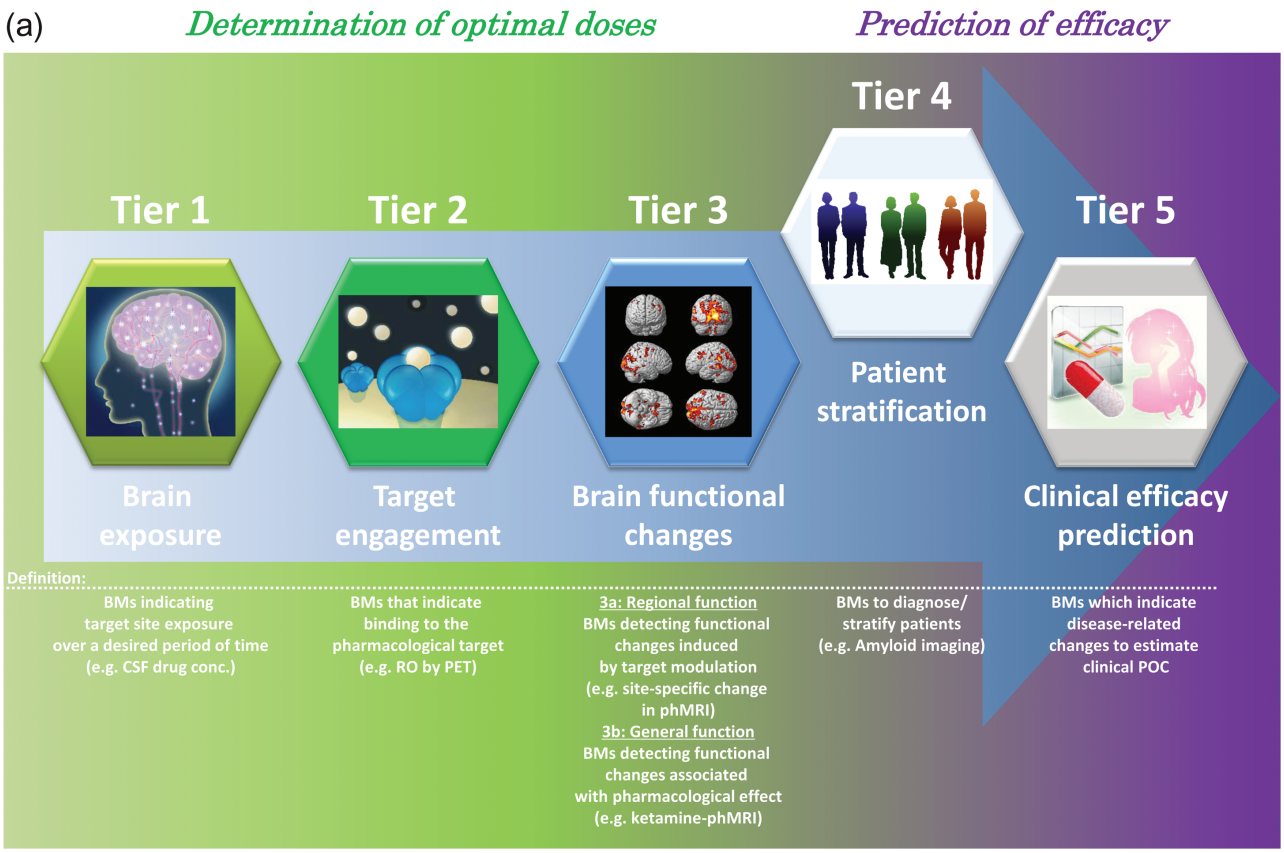
Measuring occupancy via target-specific PET probes is a well-established and accurate way to detect target engagement (Hargreaves, 2002). Occupancy data also provide some degree of confidence as to the brain exposure of a particular drug.

PET imaging has historically been successful in this regard, especially for orthosteric antagonists or enzyme inhibitors with

Table 1. Status of Biomarker Usages in CNS Disorders

Target Disease	Compound	Sponsor Collaborator	Mechanism of Action	Pillar 1	Pillar 2	Pillar 3	Nct#	References
Schizophrenia	TAK-063	Takeda	PDE10A inhibitor		PDE10A occupancy	fMRI BOLD Ketamine-induced fMRI BOLD	NCT02370602 NCT01892189	Takano et al., 2016
Schizophrenia	PF-02545920	Pfizer	PDE10A inhibitor		PDE10A occupancy	Ketamine-induced fMRI BOLD	NCT01918202 NCT01244880	
Schizophrenia	MK-0777 /TPA023	Merck & Co	GABA-Aα2/3 receptor agonist		GABA-Aα occupancy	qEEG		Atack et al., 2010 Lewis et al., 2008
Schizophrenia	bitopertin /RG1678 /RO4917838	Roche	GlyT-1 inhibitor		GlyT-1 occupancy	CSF Glycine, Event-Related Potential	NCT01116830	Martin-Facklam et al., 2013 Hofmann et al., 2016
Schizophrenia	GSK1018921	GlaxoSmith Kline	GlyT-1 inhibitor		GlyT-1 occupancy	CSF Glycine, qEEG, mismatchnegativity	NCT00945503 NCT00527020 NCT00929370	Gunn et al., 2011
Schizophrenia	MK-2637	Merck & Co	GlyT-1 inhibitor		GlyT-1 occupancy	Motor evoked potential, qEEG	NCT00934466	Joshi et al., 2015
Schizophrenia	LY2140023 /Pomaglumetad methionil	Eli Lilly	mGlu2/3 agonist	CSF PK		Ketamine-Challenge fMRI Assay, CSF monoamine metabolites	NCT01524237	Lowe et al., 2012
Schizophrenia	JNJ-40411813	J&J	mGlu2 PAM		mGlu2 receptor occupancy 5-HT2A occupancy	Sleep EEG, Ketamine-induced psychotic symptom	NCT01359852 NCT01358006 NCT01101659 NCT01951053	Ahnaou et al., 2016
Schizophrenia	AZD8529	AstraZeneca	mGlu2 PAM	CSF PK		Ketamine-induced fMRI, EEG	NCT00985933 NCT00986531	Cook et al., 2014
Depression /FXS	RO4917523	Roche	mGlu5 antagonist		mGlu5 receptor occupancy	fMRI	NCT01483469 NCT01045083	
Mild-to-moderate Alzheimer's disease	Bapineuzumab	Janssen /Pfizer	anti-amyloid antibody			amyloid PET, CSF p-tau, vMRI, FDG PET	NCT00575055 NCT00574132	Liu et al., 2015 Salloway et at., 2014
Mild Alzheimer's disease	Solanezumab	Eli Lilly	anti-amyloid antibody			amyloid in blood & CSF, tau in CSF, vMRI, amyloid/tau PET, FDG PET	NCT00905372 NCT00904683 NCT01900665	Doody et al., 2014 Siemers et al., 2016
Early Alzheimer's disease	Aducanumab /BIIB037	Biogen	anti-amyloid antibody			amyloid PET, vMRI, FDG PET, fluid biomarkers	NCT01677572	
Prodromal Alzheimer's disease	Gantenerumab	Roche	anti-amyloid antibody			amyloid PET, amyloid and tau in CSF, vMRI, FDG PET	NCT01224106 NCT01760005	
Prodromal Alzheimer's disease	Verubecestat /MK-8931	Merck & Co	BACE inhibitor	CSF PK		CSF Aβs & sAPPβ, amyloid PET	NCT01953601	
Early Alzheimer's disease	AZD3293	AstraZeneca /Eli Lilly	BACE inhibitor	CSF PK		CSF Aβs & sAPPβ, amyloid PET, tau in CSF, FDG PET	NCT02245737	

Abbreviatoins: Aβ, amyloid beta; BACE, beta-secretase; BOLD, blood oxygenation level dependent; CSF, cerebrospinal fluid; fMRI, functional magnetic resonance imaging; FDG, fluorodeoxyglucose; FXS, fragile X syndrome; GABA, gamma-aminobutyric acid; GlyT-1, glycine transporter 1; 5-HT, 5-hydroxytryptamine; mGlu, metabotropic glutamate; PAM, positive allosteric modulator; PDE10A, phosphodiesterase 10A; PET, positron emission tomography; PK, pharmacokinetics; qEEG, quantitative electroencephalography; sAPP, soluble amyloid precursor protein; vMRI, volumetric MRI.



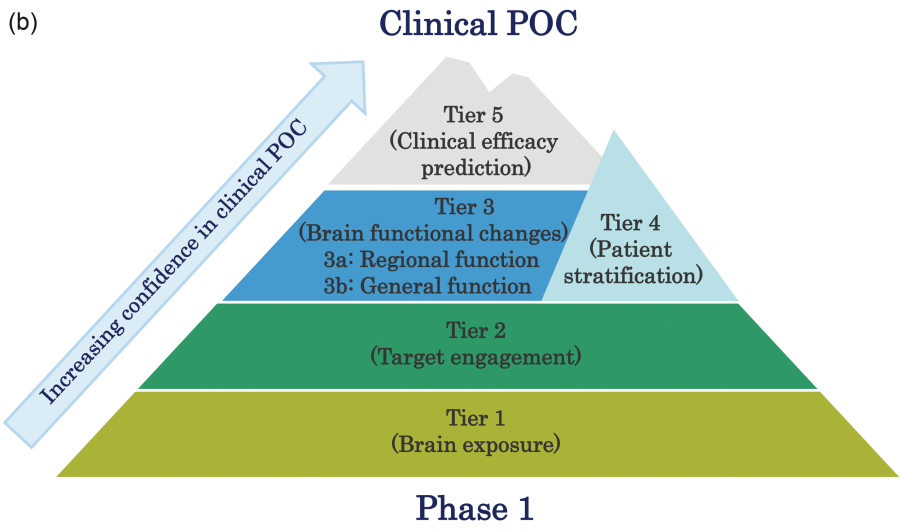


Figure 1. Redefinition of "5-Tiers" for future CNS-drug development. Each Tier can provide different degrees of evidence of biomarkers (BMs) for appropriate clinical POC studies, the efficacy of a drug, and accumulating tier-specific evidence (receptor occupancy [RO]; pharmacological functional MRI [phMRI]) portends drug action efficacy in a way that is comprehensive than previous paradigms and will lead to improved clinical POC (Fig 1a). Thus, each Tier can be considered as a milestone when climbing difficult-but-manageable peaks such as Mt. Fuji (Fig 1b).

clear relationships between target occupancy and pharmacological efficacy (Hargreaves, 2002; Le et al., 2008). However, it is difficult to apply PET imaging studies to other types of drugs, such as agonists, partial agonists, and allosteric modulators, because of complicated binding modes and low occupancies required to produce pharmacological effects (Grimwood and Hartig, 2009; O'Brien and Conn, 2016). Therefore, alternative approaches to indirectly measure target engagement based on functional or pharmacodynamic changes are discussed under Tier 3.

Tier 3: Biomarkers Detecting Brain Functional Changes

Investigation of drug-induced brain functional changes remains important, especially when specific PET tracers are not available or when drugs such as agonists and allosteric modulators are evaluated. Fluorodeoxy glucose (FDG)-PET, phMRI, and EEG are commonly used to capture drug-induced changes in neural function and cerebral metabolism. Despite their ubiquity, these methods occasionally produce nonspecific signals unrelated to the modulatory effects of the drug. Drug-induced functional

changes to the brain can be divided into 2 segments: (1) functional changes specific to brain regions where drug target molecules are highly expressed, and (2) alterations observed beyond the normal distribution of a drug target molecule, both of which can be considered a pharmacological effect of drug administration. Because evidentiary weighting may differ between 1 and 2, we propose that Tier 3 be further divided into Tier 3a and Tier 3b.

Tier 3a: Biomarkers detecting regional functional changes related to target

Signal specificity should be carefully considered by assessing, among other factors, distribution of the drug target molecule and the molecular mechanism of the drug. A region-specific functional change exhibiting a direct correlation with the distribution of the drug target molecule would naturally provide higher levels of confidence than alterations in other brain regions. For example, TAK-063, a phosphodiesterase 10A (PDE10A) inhibitor, has been reported to increase reginal blood flow in only the brain regions where PDE10A is abundantly expressed (Tomimatsu et al., 2016), indicating that functional change induced by TAK-063 may be mediated through PDE10A inhibition.

Tier 3b: Biomarkers detecting general functional changes associated with pharmacological effect

Functional changes in neural circuits may play a key role in pathogenesis of various neuropsychiatric disorders. As such, drug-mediated functional changes observed in offsite through neural circuitry may provide additional relevant information for said drug's method of action. Indications of this subclass of biomarker can be detected in healthy volunteers at earlier stages of clinical development and prove useful in bridging preclinical and clinical studies. For example, perturbation of neural circuits associated with some neuropsychiatric disorders by agents like ketamine or scopolamine can be conducted in rodents, nonhuman primates, and healthy volunteers.

Tier 4: Patient Stratification Biomarkers

Current diagnosis of neuropsychiatric disorders is defined by international guidelines and classification systems (ICD-11/DSM-5) and is based primarily on patient symptoms. Accordingly, biological heterogeneity among patients can contribute significantly to lack of efficacy in Phase II trials. To improve clinical success rates, it is essential to select subsets of patients who share biological characteristics optimal for testing candidate compounds. Empirical evidence supports this notion: a retrospective analysis of AstraZeneca's R&D projects from 2005 to 2010 revealed that projects with high confidence in patient selection demonstrated a greater likelihood of success in Phase IIb (Cook et al., 2014).

Amyloid imaging for AD provides an example illustrating this aspect of patient stratification. By imaging amyloid in patients, AD and non-AD dementia can be discriminated (Weiner et al., 2015). Therefore, it is reasonable to select patients displaying amyloid deposits when evaluating potential AD-preventive drugs.

Patient stratification biomarkers may also play a role in mechanism-based drug discovery. For example, α-synuclein accumulation is observed in both Parkinson's disease and dementia with lewy bodies (Barker and Williams-Gray, 2016), while TAR DNA-binding protein 43 kDa (TDP-43) accumulation is observed in some population of patients with both frontotemporal lobar degeneration and amyotrophic lateral sclerosis (Neumann et al., 2006). These overlapping molecular signatures may illuminate common pathophysiological pathways between different disorders, facilitating drug development aimed at common biological components of differing diseases.

Tier 5: Clinical Efficacy Prediction Biomarkers

In addition to patient stratification, establishing biomarkers that predict efficacy (i.e., exhibit a high degree of correlation with clinical symptoms) is needed to make a clear go/no-go decision in early phases of clinical studies. Indeed, Cook et al. (2014) have also reported that Phase IIa projects with an efficacy prediction biomarker had twice as much likelihood of stage-up compared with projects without such biomarkers.

Although amyloid imaging is highly useful as a diagnostic marker for AD, correlation between amyloid accumulation and clinical symptoms remains controversial (Liu et al., 2015). On the other hand, signal density in tau imaging has been reported to correlate with cognitive dysfunction and hippocampal atrophy in patients (Maruyama et al., 2013; Ossenkoppele et al., 2016). Thus, tau imaging may have the potential to be both a patient stratification marker and an efficacy prediction biomarker.

Tier 5 biomarkers require both imaging and clinical data derived from limited samples used for further decision-making.

Proposed Neuroimaging Biomarkers to Be Developed by PPPs

A number of biomarker candidates would benefit from development within PPPs. These include validated, standardized biomarkers labeling subsets of neurons (e.g., parvalbumin-positive GABA interneurons) or aggregated proteins (e.g., α-synuclein) as well as markers aimed at gauging the activity within particular neural circuits. In contrast, development of PET tracers for novel drug target molecules may not always be suited for PPPs due to conflicts of interest and confidentiality issues. Both the EU and US have established some precompetitive PPPs to improve CNS drug discovery and development, including the identification and validation of biomarkers. For example, the Innovative Medicines Initiative (Brady and Potter, 2014; Gottwald et al., 2016) program Novel Methods Leading to New Medications in Depression and Schizophrenia (NEWMEDS) has validated the use of PET tracers to measure changes in extracellular concentrations of some neurotransmitters (Finnema et al., 2015).

Biomarkers Specifically Labeling Particular Cell Types or Molecules

Markers labeling glutamatergic and GABAergic systems

Disruption of the brain's excitatory/inhibitory balance has increasingly been implicated in the pathophysiology and etiology of several neuropsychiatric disorders (including schizophrenia, autistic spectrum disorders, and prodromal neurodegenerative dementias) (Rubenstein and Merzenich, 2003; Lewis et al., 2012). Given the broad cellular subtypes involved in maintaining this balance (including NMDA receptor-positive cells and certain types of GABA- and parvalbumin-positive interneurons), imaging agents for glutamatergic and GABAergic transmissions, including radioligands for NMDA, AMPA, and GABA receptors and GABA transporters, could serve as early diagnostic markers associated with neuromodulatory and neuroprotective treatments in these disorders. Additionally, it would be important to develop or validate a magnetic resonance spectroscopy method to measure glutamate, glutamine, and GABA to comprehensively understand the molecular underpinnings of this balance.

Neuroinflammatory markers

Growing evidence suggests a prominent role for neuroinflammation in the pathology of neuropsychiatric disorders. In particular, several studies have implicated microglia, the resident immune

cells of the CNS, in the development and progression of schizophrenia, mood disorders, and neurodegenerative disorders (Réus et al., 2015). Translocator protein (TSPO) has been studied as a biomarker of reactive gliosis and inflammation in a variety of neuropathological conditions, and increased levels of this factor have been suggested as a marker for activated microglia (Sandiego et al., 2015). Therefore, TSPO PET imaging may be useful for investigating both the role of neuroinflammation in various diseases and for stratifying patients with diseases for which neuroinflammatory pathophysiology is suspected. Moreover, despite some controversy, accumulating evidence supports the existence of aggressive M1-like and protective M2-like phenotypes of microglia (Nakagawa and Chiba, 2015). TSPO is believed to be a marker for M1-like microgliosis, while other signaling molecules are linked to the establishment of other microglial phenotypes. Imaging of purinergic receptors via PET imaging could be a useful tool to monitor microglial activation, as both P2X7 and P2Y12 are evidently involved in M1-like and M2-like microgliosis (Moore et al., 2015; Iwata et al., 2016), respectively.

Oligodendrocyte markers

Dysfunction of oligodendrocytes or demyelination due to loss of oligodendrocytes has been observed in neuropsychiatric disorders such as schizophrenia and multiple sclerosis (Prineas et al., 1984; Hof et al., 2003). Status markers labeling oligodendrocytes or oligodendrocyte precursor cells are useful tools for understanding diseases in which oligodendrocyte abnormalities are involved and for stratifying these patients. Development of PET tracers that bind molecules specifically expressed in oligodendrocytes (S1P5) or oligodendrocyte precursor cells (GPR17) would also be useful.

Markers for aggregated proteins

Among markers for aggregated proteins, amyloid imaging has been extensively explored for diagnostic purposes in AD, while tau imaging has been employed in studying tauopathies. Other examples being actively explored include PET tracers for α-synuclein (for α-synucleionopathies) and TDP-43 (for TDP-43 proteinopathies).

Validation and Standardization of Methods to Measure Brain Function

FDG-PET, functional MRI (fMRI) and EEG have all been used to measure brain function, via measurement of different biological signals. These approaches can distinguish neural network aberrancies induced by psychotomimetic drugs such as ketamine and scopolamine. These changes may represent translatable biomarkers, as these alterations frequently resemble abnormalities observed in certain pathological conditions (Molchan et al., 1994; Jones et al., 2012; Hegedűs et al., 2015; Joules et al., 2015). However, the above-mentioned methods are not fully validated and standardized, introducing the potential for contradictory results. To avoid this, uniform guidelines to validate and standardize are necessary in a clinical setting.

Example of development of imaging biomarkers by PPPs

Given that the TSPO has been observed in higher density in activated microglia across various brain diseases, TSPO PET tracer can be used in a wide range of diseases in which neuroinflammation is implicated (Yasuno et al., 2008; Takano et al., 2010). To date, several TSPO PET tracers have been developed, but the use of existing radioligands has been complicated by the existence of low- and high-affinity binders (Kreisl et al., 2010) that has been ascribed to a single nucleotide polymorphism (rs6971) (Owen et al., 2012). The resulting heterogeneity has led to inconsistent results and has complicated interpretation of this data (Kreisl et al., 2013; Bloomfield et al., 2016; Coughlin et al., 2016). The development of a novel PET tracer of TSPO that is unaffected by genetic variability would be of great use in determining drug intervention timing (e.g., illness phase specific pharmacotherapy) for neuropsychiatric disorders in which inflammatory processes are involved.

Summary and Future Directions

To improve the success rate of INDs in the CNS field, we have proposed the expansion and reorganization of existing biomarker utility measures into a 5-tiered indices covering the following functional facets: Tier 1 (brain exposure), Tier 2 (target binding), Tier 3 (brain functional changes), Tier 4 (patient stratification), and Tier 5 (clinical efficacy prediction).

Further rollout of biomarkers is imperative for improvement in clinical development, particularly in the field of psychiatry. Failures of INDs in the CNS field are largely due to small overall effect and/or failure to attain primary endpoints set for clinical trials. For patients diagnosed by the current ICD-10/DSM-5, the general assumption is that patients suffering from schizophrenia, bipolar disorder, and major depression can be composed of biologically distinct subpopulations with heterogeneous pathophysiology. Thus, INDs targeting a selective mechanism could be beneficial to only a fraction of the entire patient population. Currently available drugs for schizophrenia share one selective mechanism, the blockade of the dopamine D2 receptor (Farde et al., 1988). Although blocking D2 receptors is widely effective in schizophrenic populations, patient subgroups exhibit a wide range of responses to these drugs (Demjaha et al., 2012). If we apply neuroimaging data prospectively to exclude treatment-resistant patients (vis-à-vis Tier 4), the effect size for a given compound could increase. Because neuroimaging biomarkers that predict clinical efficacy might depend on biological pathways disturbed in patients, Tier 5 (clinical efficacy prediction) criteria could be tightly linked to Tier 4. As discussed above, neuroimaging biomarkers monitoring the status of excitatory/inhibitory balance, neuroinflammation, and oligodendrocytes also represent potential candidates to benefit from the use of Tier4/5 biomarkers. It is important to remember that the cost and effort involved in neuroimaging biomarkers renders them unsuitable for large-scale clinical trials; therefore, biomarkers that are less costly and easier to measure than neuroimaging biomarkers may be needed in later trials.

Although it remains largely outside the scope of this working group's report, PET may also be used to predict safety/tolerability; microdosing of labeled therapeutics could indicate drug predisposition for accumulation in certain organs, allowing advanced prediction of possible side effects (Roberts et al., 2015; Papadimitriou et al., 2016; Burt et al., 2016).

In summary, neuroimaging biomarkers are ever-more-powerful tools for evaluating the potential of INDs. To better support this mission, we propose redefinition of existing criteria to further the use of biomarkers as shepherds of clinical development, while implementing a fourth (patient stratification) and fifth (clinical efficacy prediction) tier to this index. Our ultimate objective is to improve the success rate of INDs and eventually to achieve true "precision medicine" in CNS disorders. This includes addressing emerging problems, including symptom- or mechanism-specific biomarkers used for diagnosis and stratification. We also propose to pursue generation and development of new neuroimaging biomarkers through PPPs that combine disease knowledge, cutting-edge technologies, chemical

libraries, medicinal chemistry, and funding to achieve novel breakthroughs. Considering their potential to accelerate drug discovery in the CNS field, PPPs should also include regulatory agencies, such as U.S. Food and Drug Administration, Eurpean Medicines Agency, and Pharmaceuticals and Medical Devices Agency so as to standardize application of neuroimaging biomarkers and their related general biomarkers in clinical trials of INDs and frame how they may be used to stratify target patients and reach primary and co-primary endpoints.

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Statement of Interest

Drs. Chaki and Omura are employees of Taisho Pharmaceutical Co., Ltd. Drs. Kimura and Furusawa are employees of Takeda Pharmaceutical Co., Ltd. Drs. Matsumoto and Miyoshi are employees of Astellas Pharmaco Inc. Drs. Ogura and Yamamoto are employees of Eisai Co., Ltd. Dr. Negishi is an employee of Mochida Pharmaceutical Co., Ltd. Dr. Saijo is an employee of Mitsubishi Tanabe Pharma Co. Dr. Watanabe is an employee of Daiichi Sankyo Co., Ltd. Dr. Nakatani is an employee of Chugai Pharmaceutical Co., Ltd. Dr. Liou is an employee of Ono Pharmaceutical Co., Ltd. Dr. Walton is an employee of Astellas Research Institute of America LLC.

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