A strategy for developing new treatment paradigms for neuropsychiatric and neurocognitive symptoms in Alzheimer’s disease

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Successful disease modifying drug development for Alzheimer’s disease (AD) has hit a roadblock with the recent failures of amyloid-based therapies, highlighting the translational disconnect between preclinical animal models and clinical outcome. Although disease modifying therapies are the Holy Grail to pursue, symptomatic therapies addressing cognitive and neuropsychiatric aspects of the disease are also extremely important for the quality of life of patients and caregivers. Despite the fact that neuropsychiatric problems in Alzheimer patients are the major driver for costs associated with institutionalization, no good preclinical animal models with predictive validity have been documented. We propose a combination of quantitative systems pharmacology (QSP), phenotypic screening and preclinical animal models as a novel strategy for addressing the bottleneck in both cognitive and neuropsychiatric drug discovery and development for AD. Preclinical animal models such as transgene rats documenting changes in neurotransmitters with tau and amyloid pathology will provide key information that together with human imaging, pathology and clinical data will inform the virtual patient model. In this way QSP modeling can partially overcome the translational disconnect and reduce the attrition of drug programs in the clinical setting. This approach is different from target driven drug discovery as it aims to restore emergent properties of the networks and therefore likely will identify multitarget drugs. We review examples on how this hybrid humanized QSP approach has been helpful in predicting clinical outcomes in schizophrenia treatment and cognitive impairment in AD and expand on how this strategy could be applied to neuropsychiatric symptoms in dementia.

We believe such an innovative approach when used carefully could change the Research and Development paradigm for symptomatic treatment in AD.
Many drugs failed in Phase II proof-of-concept, some failed in Phase III pivotal trials.

| Drug Mechanism | Clinical Phase |
|----------------|----------------|
| Amyloid-beta modulation | Passive vaccination |
| Bapineuzumab | PhIII |
| Solanezumab | PhIII |
| Semagacestat | Gamma-secretase inhibitor |
| | PhII: irreversibly worsens cognition |
| Aavagacestat | Gamma-secretase inhibitor |
| | PhII: irreversibly worsens cognition |
| Ponezumab | Passive vaccination |
| | PhII |
| Tiampirostat | Plaque destabilizer |
| | PhIII |
| Sicylo-nositol | Block Abeta accumulation |
| | PhII |
| Tarenflutol | Abeta lowering agent |
| | PhII |
| Neuroprotective | Mitochondrial stabilizer |
| Lamotroprine (dimebon) | PhII |
| PF-04494700 | RAGE inhibitor |
| Cevelmeline | Sensitizes neurons to growth factors |
| | PhII |
| Slideniene | Anti-oxydant |
| | PhII |
| Zlooprofin, naproshen, rolocob | Anti-inflammatory |
| | PhII |
| Alenavastatin, simvastatin | Cholesterol modulation |
| | PhII |
| Leuprolide, neurotin | Modulates growth factor |
| | PhII |
| Rasiglazine | PPAR agonist |
| Sabeluzole, T817-MA | Neuroprotectant |
| | PhII |
| Symptomatic Treatment | Neurotransmitter modulator |
| H3 antagonism, indopine, LU25-109, H4 agonism (PRX-03040), NS2300, ST101 | PhII |
| Iaproncine, T06683 | A4b2 nAchR modulator |
| C8518 | AMPARine |
| Eptastigmine, hupcrine, metrifronate, phenserine, physostigmine, propytofore | ACHe inhibitor |
| MEM1003 | PhII |
| Milameline, subacrine, xamuloline, NGX267 | Ltype Ca channel inhibitor |
| MKC-231 | Partial mAChR agonist |
| SGS-742 | GABA-B antagonist |
| Suriltozole | Inverse GABA agonist |
| Nafiracetam, piracetam | Cognitive enhancer |
| | PhII |
| Neramexane | NMDA antagonist |
| | PhII |

Such a symptomatic effect is also important for off-target effects of possible disease modifying compounds; any off-target pharmacology that would reduce cognitive performance can lead to a failed clinical development program, even if the biochemical effect on the primary target is met. An example is dimebon, a mitochondrial stabilizer molecule (Eckert et al., 2012) which shows neuroprotection is preclinical models (Steele et al., 2012), but failed to show an effect in large phase III trials in AD (Berrozavanny, 2010). Close study of its total pharmacology against the human receptors (Okun et al., 2010) reveals significant dopamine genotype-dependent anti-cognitive off-target effects that probably significantly reduces the clinical signal in ADAS-Cog (Geerts, 2012).
improve the neuropsychiatric symptoms but it is unclear whether this is a specific effect or secondary to a cognitive improvement.

In the absence of specific drugs for this indication, clinical trials are performed with drugs that have been approved for other indications. For instance, a 6 week clinical trial in 67 AD patients with apathy treated with methylphenidate (Mintzer et al., 2012) suggested a trend for improvement of 2.5 points on the AES (Apathy Evaluation Scale), and a significant improvement on clinical global impression of change (CGIC; 3.7 points) and on neuropsychiatric inventory (NPI).

The ideal treatment combination would be a multi-pharmacology profile that combines symptomatic improvement (for instance on the ADAS-Cog scale or NPI) with a disease modifying activity. This can substantially de-risk the whole research and development (R&D) project, as clinical trials can be executed using relatively short durations (26 weeks) and market approval can be sought based upon symptomatic improvement. Once on the market, long-term clinical trials or extensive studies using biomarkers can be performed to prove the disease modifying effect. This has the additional advantage that patent life can be used to its full extent.

This suggests that symptomatic treatment for cognitive or neuropsychiatric problems has an important place in the full Research and Development portfolio for AD.

PRECLINICAL MODELS FOR COGNITIVE ENHANCERS

Traditional cognitive tests such as object recognition, T-maze, set shifting, and Morris water maze have been performed for a long time leading to an impressive literature and a profound understanding of the (rodent) brain neurophysiology that leads to the observed outcomes. When coupled with animal models that reflect part of Alzheimer pathology, reversal of a cognitive deficit can be demonstrated with many candidate drugs. Many of these same drugs do not work in the clinical setting (Thomsen et al., 2010). Possible solutions discussed at a recent workshop, “Improving the utility and translation of animal models for nervous system disorders”, on this topic organized by the Institute of Medicine (http://www.nap.edu/catalog.php?record_id=13530) include bringing in aspects of human clinical trial management, such as power calculations, standard operating procedures, blinding of observers and comedication into the preclinical world in addition to a more organic integration of quantitative systems pharmacology.

Another issue is the alignment of preclinical test readouts and human clinical scales. In the field of cognitive impairment associated with schizophrenia (CIAS), The National Institutes of Health (NIH)-sponsored meetings between Food and Drug Administration (FDA), academia and industry led to the adoption of the clinical Matrices scale and the identification of preclinical animal readouts that would correspond to the different clinical dimensions (for a review see Young et al., 2009). The recently launched NewMeds Initiative supports the validation of more relevant readouts in rodent preclinical animal models using touch screen technology (Bartko et al., 2011) in an attempt to bridge this translational disconnect.

While many of these ideas will improve the reproducibility of preclinical animal test within different laboratories, it is unclear whether this will lead to improved success in the clinical development phase. There are still fundamental differences linked to the choice of rodents as preclinical animal models. For instance in the field of cognition, there is increasing evidence that the excitatory-inhibitory (ε-α) balance in cortical and hippocampal networks is fundamentally different between primates and rodents (Povysheva et al., 2008), in that monkey basket interneuron cells have a higher input resistance and a lower firing threshold, and they generated more spikes at near-threshold current intensities. In the rodent, gamma-aminobutyric acid (GABAergic) neurons represent only about 15% of all cortical neurons (Baulieu, 1993), while in the macaque monkey they represent up to 20% in visual cortex and 25% in other cortical areas (Hendry et al., 1988; Baulieu et al., 1992). Different interneuron subtypes with short spike duration are found in the primate cortex, which is not typical for rodent adapting cells (Zatsev et al., 2009). Furthermore, the developmental shift in GABA(A) receptor alpha subunit expression continues through adolescence in primate cortex, but not in rodents, suggesting species difference kinetics of GABA neurotransmission (Hashimoto et al., 2009).

PRECLINICAL MODELS FOR NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER’S DISEASE

While there are many preclinical models and readouts for cognition, there are almost no animal models that are typically developed for neuropsychiatric behavioral symptoms in dementia. Neuropathological studies indeed suggest a profound and mostly tangle-driven locus coeruleus (LC) pathology early on in the disease (Palmer and DeKosky, 1993; McMillan et al., 2011) and additional LC pathology through treatment of mice with N-(2-chloroethyl)-N-ethyl-bromobenzylamine (DSP4) can exacerbate olfactory dysfunction in traditional amyloid precursor protein (APP) transgene mice (Rey et al., 2012).

The dorsal raphe (DR) also shows neurofibrillary tangle pathology (Grizberg et al., 2009) at an early stage where entorhinal cortex pathology is not yet fully established, although an imaging study in patients suggest that postsynaptic neuronal cell loss occurs before loss of serotonergic projections (Marnet et al., 2012). This is in line with the observation that DR pathology is observed more in tauopathy transgene mice than in amyloid-related transgene mice; for instance DR pathology in the F301L tau transgene mice leads to serotonin metabolism and breathing activity changes (Menaut et al., 2011).

This suggests that brainstem pathology in serotonin and noradrenergic nuclei, in principle can be observed in specific tau transgene animal models and further exacerbated either by neurochemical or behavioral means For instance, chronic stress, induced by isolation and chronic restraint can lead to additionally monoamine dysfunction (Ieong et al., 2006; Cuadrado-Tendor et al., 2012). However, most behavioral readouts were focused on cognitive impairment rather than mood states. In addition, due to the emphasis on amyloid-based models, not many studies have been performed on relevant behavioral readouts in tau transgene mice.

Possible readouts in preclinical animal models include the resident-intruder test for aggression, locomotor hyperactivity; forced swim test and tail suspension test for depression and...
saccharine preference or progressive ratio for reinforcement for apathy. This overview suggests that mono-amine dysfunction is present in the early stages of the disease, is dominantly tau pathology driven and can affect the behavioral problems associated with dementia. This would suggest that in order to develop an R&D strategy with preclinical animal models requires a shift from amyloid-based models to tau-based models and from purely cognitive readouts to readouts that probe mood dysfunction. However some transgene APP mouse models also show behavioural disturbances, such as the 3xTg-AD model (Sternicuè et al., 2010) that might be an interesting animal model as it combines both APP and tau pathology.

However, even when achieving face-validity at the level of neuropathology in animal models, possible drug discovery could still be substantially impaired because of the species differences in receptor distribution and neuromodulator synapse physiology. For instance the striatal dopaminergic synapse is substantially different between rodent and primate (Spiros et al., 2010), to the extent that this led to the clinical failure of the partial D2 agonist bifeprunox, despite the fact that this compound achieved a higher efficacy in preclinical rodent-based animal models than the similar successful drug aripiprazole. Also, the distribution of the 5-HT3R, a receptor involved in negative symptoms in schizophrenia (Akhouroundad et al., 2009) and in attention deficit (Lennertz et al., 2010) is fundamentally different between mice and men (Hewlett et al., 1999; Marazzini et al., 2001), suggesting that changes in serotonin tone can lead to very different behavioral outcome.

QUANTITATIVE SYSTEMS PHARMACOLOGY
The previous discussion suggests that improved translation can be achieved by developing a hybrid computer-based model that combines the best of preclinical neurophysiology with actual human imaging, postmortem, and clinical data. Such an approach is based upon a biophysically realistic computer model of neuronal networks that takes into account proper target engagement of central nervous system (CNS) active drugs and well documented effect of receptor activation level changes on ion-channel conductances that ultimately modulate neuronal excitability and timing of action potential generation (Geerts, 2012). In addition calibration of the biological coupling parameters using the correlation between clinical outcomes and the outcomes of the same drugs in the computer platform ensures a tight clinical association between model output and actual anticipated clinical result.

Details of the platform have been described elsewhere (Spiros et al., 2010; Roberts et al., 2012b). With regard to cognitive disorders, we have used this platform to explain the differential clinical effect of memantine and apolipoprotein E (APOE) on ADAS-Cog and compare this to the clinical outcomes, and (5) use this virtual patient model to perform in silico screening.

STRATEGY FOR A NOVEL PRECLINICAL MODEL OF BEHAVIORAL PROBLEMS ASSOCIATED WITH DEMENTIA
We propose to combine preclinical neurophysiology, human neuropathology, and human clinical data in a mechanism-based computer model for developing new drugs for the BPSD. We outline a strategy aimed at (1) documenting better the neuropathological changes in modulatory neurotransmitters in AD by studying the effects of AD pathology on LC, DR, and ventral tegmentum area, preferably in transgene rats, (2) comparison with the neuropathology observed in human patients, especially with regard to functional connections between different brain regions, (3) build a computer model of these interactions based upon the human imaging template but informed by the neurophysiological changes in cellular excitability observed in transgene rats and (4) identify and calibrate emergent properties of the network model by simulating various clinical trials with CNS psycho-active drugs and compare this to the clinical outcomes, and (5) use this virtual patient model to perform in silico screening.

Below, we expand on different steps.

DERIVING INFORMATION FROM PRECLINICAL ANIMAL MODELS
Preclinical data from transgene rats (Li et al., 2008) are preferred because of LC and DR size considerations and because electro-physiology of the rat striatum can be done in awake animals (Li et al., 2012). Lentivirus-mediated gene transfer with mutant tau (Khandelwal et al., 2012) can enhance the pathology in the LC and DR. The striatal dopamine system is an important part of the...
A large number of imaging studies have been performed in the computational thalamus model (Bazhenov et al., 1998) to extend negative symptoms in schizophrenia (Geerts et al., 2013). Pharmacological interventions, such as Glycine transporter-1 inhibitor in combination with neurophysiology data on glycine dynamics, a model has been developed to delineate the functional brain networks in various psychiatric conditions (Williamson and Allman, 2012), identifying emotional encoding, representational brain and directed activity increases the maximum conductance of Leak channels in TC cells and the maximum conductance of h channels in TC cells and the maximum conductance of Leak channels in Re cells.

The spiking properties of TC neurons is caused (Traub et al., 1991) by a fast sodium channel, a fast potassium channel, a low-threshold Ca channel, a hyperpolarization-activated cation channel, a potassium A channel, and a potassium leak channel. To model an RE cell, a fast sodium channel, a fast potassium channel, a low-threshold Ca channel, and a potassium leak channel are included. Background noise caused by synaptic bombardment by excitatory and inhibitory neurons is represented by a stochastic model (Destexhe et al., 2001) containing two fluctuating conductances. Muscarinic M3 receptor activation increases the maximum conductance of h channels in TC cells and the maximum conductance of Leak channels in Re cells.

The thalamic component (Figure 2). The synaptic interaction between these neuronal types, and their intrinsic membrane properties, leads to oscillations and suppression of multiple input signals.

The cortical network model for cognitive function is described in detail elsewhere (Roberts et al., 2012b). Basically, we extended a biophysically realistic model of a network comprised of four-compartment pyramidal cells and two-compartment GABA interneurons (Durstewitz et al., 2000; DeFelipe, 2002) with the receptor physiology of 18 different dopaminergic, serotonergic, noradrenergic, and cholinergic receptors to a system of 80 four-compartment pyramidal cells and 40 two-compartment interneurons (Figure 2). An mGluR5-dependent delayed afterdepolarization current that can increase the spiking rate of pyramidal cells for several seconds was implemented as an alpha function in the model with a time constant similar to the observation in (Sidtis et al., 2009). In contrast to the original network, 40% of the interneurons do not synapse with pyramidal cells but form a small local recurrent network, based on insights from the relative number of pyramidal cells and interneurons (DeFelipe, 2002).
A stimulus is initiated by injecting a current at $t = 2000 \text{ ms}$ which starts the firing of the target pyramidal cells. Without further stimuli, this synchronized firing pattern goes on for a certain amount of time before it gets degraded by the background noise and the interference of the distractor neurons. This time span, called the working memory span, is usually in the range of $4-10 \text{ s}$ and corresponds to the time certain pattern is held in working memory (Levy and Goldman-Rakic, 2000).

A time span, called working memory span, is defined as the time a synchronous firing in the neurons that are stimulated is sustained without further stimulation. We first divide the time axis in bins of $200 \text{ ms}$ and count the number of neurons firing in that time window and determine the time points where this number exceeds $\frac{M}{2}$, where $M$ is the number of neurons stimulated at $t = 2000 \text{ ms}$. The time difference between these two transition points is the memory span.

In general, we assume a linear normalized relationship between receptor activation and biological effect on physiological responses such as $X_Y^P = \frac{X_Y^A - X_C^A}{X_Y^C - X_C^A}$, where $X_Y^A$ and $X_Y^C$ are the actual activation levels of receptor $X$ subtype $Y$ (for instance $5$-HT$_6$) after treatment ($A$) and the untreated (healthy) control levels ($C$).

The parameters coupling the documented intracellular processes with these receptors are further calibrated using the correlation between the effect of therapeutic interventions in the network and their clinical working memory performance on the ADAS-Cog scale in Alzheimer’s patients (see below).

Alzheimer’s disease pathology is implemented as a loss of cortical neurons (Ball, 1977) at a rate $\text{Neuron\_Loss (\% per week)}$ and synapses from pyramidal neurons (Masliah et al., 1989) with a rate $\text{Synapse\_Loss (\% per week)}$. Both excitatory-excitatory (e-e) and e-i are eliminated at the same rate, but because there is an additional pyramidal cell loss, e-e synapses tend to decrease faster.

Reduced cholinergic tone (Davies and Maloney, 1976) is implemented as a free parameter $A_{\text{Ch} \_\text{decrease}}$ on all cholinergic receptors (M$_1$ and M$_2$ mAChR, and $\alpha_7$ and $\alpha_4 \beta_2$ nAChR). In addition we introduce a placebo effect at week 12 using an increase in general cortical dopaminergic tone (Boileau et al., 2007). The size of the DA placebo effect is calibrated as well.

LC and DR pathology will be implemented as derived from human neuropathology data. Basically the decrease in norepinephrine (NE) tone as a consequence of noradrenergic tau pathology will be reduced by a compensatory mechanism (McMillan et al., 2011), that however, will get smaller as the...
FIGURE 2 | Circuitry and receptor effects for the proposed cortical-basal ganglia-thalamic model. A working memory subcircuit (Durstewitz et al., 2000) maintains a burst of activity representing working memory span. Two types of medium spiny neurons in the striatum (Gruber et al., 2003), D1 and D2 project inhibitory (−) synapses to GPi (direct pathway) and GPe (indirect pathway) respectively. The GPe neurons are reciprocally coupled to themselves and the subthalamic nucleus (STN; Rubin and Terman, 2004; Pirini et al., 2009). The STN projects excitatory (+) synapses to the GPi and the GPe; projects inhibitory connections to the thalamus (Bazhenov et al., 1998). Thalamocortical (TC) neurons excite reticular (Re) neurons that reciprocally inhibit TC. Sensory input excites TC and TC projects to the cortex. All cell types receive background excitatory and inhibitory fluctuating inputs that represent random synaptic activity. White rectangles represent membrane currents and colored ovals represent receptor types.

development driven by the fact that these symptoms drive a large part of the economic costs associated with institutionalization.

Target driven discovery paradigms in general have resulted in disappointing clinical outcomes; in fact a retrospective study (Swinney and Anthony, 2011) of FDA-approved medications over the last 10 years and over all indications has found that a majority of successful drugs have been identified using phenotypic assays, despite a tremendous investment in reductionist genomic-based approaches. While this study does not explicitly mention CNS indications, it is safe to assume that in these indications, target-derived approaches are even less successful. However, a phenotypic assay for CNS indications likely has a very low throughput and...
includes rodent or non-human primate models. As a notable exception, the company psychogenics has optimized a relatively high-throughput behavioral platform (Bartko, S. J., Venturelli, I., Saksida, A. H., et al., 2009). Added ondansetron for stable schizophrenia: a double blind, placebo controlled trial. Schizophrenia Res. 107, 206–212.

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