Introduction

CNS drug development presents unique challenges not appreciated by the FDA or Institutional Review Boards (IRBs). These challenges are associated with extraordinary expense and development time. CNS disorders are more complex than other diseases because clear-cut drug (gene or mutation) targets are elusive (multiple and different) and susceptibility genes are present in different patients, plus there is a significant environmental impact, no true animal models, and the lack of quantitative measures for cognitive disruption. Target driven approaches derive from human genetic and transcriptional profiling studies and may involve transgenic animals and RNAi studies. An alternative approach used behavior driven screening and both approaches were discussed at this meeting.

This report covers the psychiatric track which was focused on approaches to define and the progress on imaging, behavioral, and molecular biomarkers for CNS disease, cell culture and animal models, new drugs and drug targets, and proteins and pathways. The meeting had five sponsors (Cambridge Cognition, ExonHit, EnVivo Pharmaceuticals, NeuroDetective and Precision Med), and approximately 200 participants in total. The speakers were from two large and nine small pharmaceutical/biotechnology companies, two research organizations, and five universities.
Costs and success rates

Smita Price (Curidium Medica) reported data from the Centre for Medicine Research that showed the probability of success across all phase I, II and III was significantly lower for CNS diseases (1, 2 and 14%, respectively), than for anti-infectives (33, 47, 75%, respectively), cardiovascular disease (6, 9 and 43%, respectively), and oncology (6, 8 and 32%, respectively). Dr Price reported on data showing the total average developmental costs per drug, and average clinical development times for CNS therapeutics were $537 million and 115 months, respectively; while anti-infectives, cardiovascular and analgesics/anesthetic average $492 million and 82 months, $460 million and 63 months, and $375 million and 62 months, respectively. Despite these substantial drawbacks the CNS market is large (> $60 billion in 2005 and approximately $12 billion in 2004 for antipsychotics alone), and a 'winner take all' endeavor. A future global pharmaceutical market driver is personalized medicine. CNS diseases are clear targets for this approach because of disease complexity, current diagnosis being based on clinical signs and symptoms, and there generally being a low patient response and substantial side effects. CNS drugs particularly are a compromise of efficacy versus side effects.

Angelo Sambunaris (Atlanta Institute of Medicine and Research) provided a unique and thoughtful presentation on how to improve the success of clinical trials for CNS drugs, and discussed how current clinical testing approaches contribute to drug development costs. Factors that contribute to negative and failed trials including complex trial designs, rising placebo response rates, changing study-subject populations, inadequate/inappropriate screening procedures, uneven rater performance, and limited test population demographics. Suggestions for improvements include sponsor corporate administration and financial values that allow the selection of clinical research organizations (CROs) with extensive, successful clinical trial experience including a 'hands-on' principle investigator (PI). Close contact between the sponsor and CRO should include a legal contract that specifies the responsibilities of each and collaboration on the study design. A meaningful monitoring of the CRO by the sponsor must include insurance of compliance with the test design and the developed standard operations protocol (SOP), and insurance that follows good clinical practice (GCP), and has IRB and ethical reviews. FDA document FD1572 is an agreement between the clinical investigators/sub-investigators and the FDA, and not an agreement between the sponsor and investigators/sub-investigators. Only and all decision makers in the clinical trial aspects at the CRO should sign document FD1572.

Recommended clinical design study changes include: i) educating the local IRB that CNS investigations cannot follow study protocols developed for other diseases; ii) changing from a clinical referral to recruitment form; iii) increasing the spectrum of patients participating by modifying the IRB exclusion/inclusion category; iv) decreasing the number of competing sites by increasing the number of selective sites with a history of completing clinical studies and having the needed expertise; v) increasing payments to clinical research centers and decreasing payments to individuals; vi) using a sliding scale of payments reflective of individuals' expertise; vii) never paying for patient recruitment number; viii) using clinical raters only (eg, certification of non-profession is not a substitute); ix) collecting efficacy data using multiple primary and secondary tools; x) ensuring the research staff operates as a team rather than as adversaries; and xi) having the CRO document not only errors but also corrective measures and improvements.
Biomarkers for CNS diseases

Biomarker discovery for CNS diseases, especially within the neuropsychiatric arena, is difficult because diagnosis and treatment is based, to a large extent, on self-reported human behavior, patient drug response is slow, most patients are undergoing polydrug regimes, animal models are not true mimics of disease, and the treatment response of well controls is not a reliable predictor response of ill humans.

Stratification of patients

Director of The Biomarkers Consortium at the National Institutes of Health (NIH) C Anthony Altar provided several examples of where biomarkers have helped, or will help, in the stratification of patients, including apolipoprotein E alleles, PET imaging of amyloid, use of 11C-labeled ligands binding to microglia to detect HD CAG expansion mutations, liability to drug side effect (eg, valvular heart disease associated with stimulation of the 5-HT2B receptor), and antidepressant effects (eg, citalopram-linked serotonin 5-HT2A receptor gene alleles).

The newly formed Biomarker Consortium (http://www.biomarkersconsortium.org), a collaboration between governmental (NIH, FDA) public (PhRMA, CMS, advocacy groups, non-profits), and industry (pharmaceutical and biotechnology) managed by the NIH is focused on 'pre-competitive' research that will speed discovery, development, validation of biomarkers, therapies diagnosis and treatment of disease. The AD Neuroimaging Initiative (ADNI), the largest NIH study on AD, focuses on neuronal, imaging and cerebral spinal fluid (CSF), and blood markers. The results of this study will be made public, and the FDA may give greater weight to ADNI evaluated biomarkers in drug development studies.

Schizophrenia biomarker development

Cognitive deficits are core attributes of schizophrenia and important targets for therapy. Currently, there is no registration track with the FDA for cognitive impairment and no effective treatment. Hence, quantitative validated measures of cognitive deficits are needed to measure drug efficacy, define populations, and provide reliable endpoint measures for clinical trials. The NIMH sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia/Treatment Units for Research on Neurocognition in Schizophrenia (MATRICS/TURNS) initiative provides guidelines for developing and applying cognitive markers. MATRICS (http://www.matrics.ucl.edu) recommendations for clinical trials measurements on cognition include good test-retest reliability, utility as a repeated measure, to reflect meaningful improvement/functional outcome, ability to differentiate between drugs, and to be practical and tolerable to the patient. The MATRICS developed a consensus battery of seven study domains with 10 paper tests. Although current paper tests are prone to error, there are eight academic centers participating in the ongoing TURNS (http://www.tURNS.ucla.edu) study of AD. The guidelines for this study call for patients with few symptoms other than cognitive impairment, exclusion of patients treated with more than one drug, inclusion of pharmacokinetic and pharmacodynamic measurements, and assessment of cognitive symptoms using one or more or measures. However, how to obtain clinically meaning functional data is still an issue.

Computerized tests are simple to use, easy to administer, non-confrontational, can increase
accuracy and speed of measurement, record multiple factors (eg, latency, error), provide standardized test conditions (important for multiple site studies), are free of language and culture issues, and of graded difficulty (subject test is limited when maximum performance is reached (ie, multiple errors are recorded). Laura J Back (Cambridge Cognition) reported on the development of a battery of computerized cognition tests, named Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB tests are designed for phase II and III clinical trials and are given over a 60-min period with one to two tests for each of the MATRICS domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem-solving and social recognition). Today, there are 44 publications that have used the CANTAB to evaluate schizophrenia patients. Examples were discussed that linked specific CANTAB tests to brain regions through imaging studies, specific deficits (memory, cognitive, negative) in schizophrenia, first psychosis, and dementia Alzheimer's type as well as brain damage in specific regions, and drugs known to alter cognitive symptoms in patients. CANTAB has a set of tests for emotional cognition test: anger associated with the dopamine system, anger and disgust associated with the cholinergic system, and sadness, anger and fear associated with the noradrenergic system. These tests appear to predict emotional processing and social behavior.

The CANTAB battery was used to assess childhood and adult attention deficit hyperactivity disorder (ADHD) and to evaluate response to methylphenidate (MPH), modafinil and atomoxetine. Dr Black's colleague Andrew Blackwell described how ADHD is characterized by impulsivity, hyperactivity, and inattention. Usually 3 to 7%, and up to 20%, of students in school are diagnosed with ADHD, and recent studies show that ADHD can extend into adulthood. The core defects in ADHD measured by the CANTAB are visual memory, working memory, attention, impulsivity and decision. MPH improved visual-spatial memory only. In control adults, MPH increased the stop signal response time (SSRT), modafinil led to improvements in other cognition tests, and atomoxetine had no effect.

Investigation at Psychogenics

Paul McGonigle of Psychogenics reported on the development of an automated behavioral testing system that uses complex signatures to interpret or translate behavior, and predicts clinical usefulness of novel compounds. Over 2000 behavioral features (including activity, spatial patterns, spontaneous behavior, reactive behavior, behavioral transitions, side effects) are collected automatically using reference compounds belonging to drug classes such as tricyclic antidepressants (TCAs), typical antipsychotic, psychostimulants, inactives, antidepressent, and atypical antipsychotics. The difference between the test compound and the vehicle are recorded. The signatures established with the training set were tested for robustness using a blinded set of known drugs. The system can screen around 1,000 drugs per year.

Psychogenics uses computational methods to select potential drugs from a collection of approximately 50,000 molecules using criteria such as oral bioavailability, brain penetration, drug-like properties (Lipinsky's rule of five), and no undesirable groups. Of 250 compounds screened, 50 (20% success rate) had potential behavior effect, 44 were available for confirmation, 30 active in one test, 11 confirmed in two tests, and nine had novel or unknown targets. For instance, PG-10014 and PG-100025 were as effective as sertraline in the forced swim test, and PG-100025 exhibited anxiolytic and stress reducing activity.

Selection of new compounds was improved using computation filters to pick drugs for testing
that have diverse signatures and are representative of drug clusters, and by using test results to improve selection criteria. For instance, the use of computational filters to screen 144 drugs led to almost a 2-fold increase in hits per step: 48 hits (33% success rate), 44 were available for confirmation, 29 were active in at least one test, 11 active in two tests and nine had novel or unknown identity. Compounds under optimization are PG-100092, PG-101050, PG-101035, PG-101200, PG-101044, PG-101159 and PG-101108. Optimization includes testing of drug combinations.

**Molecular biomarkers**

Several reports were presented about the use of mRNA expression profiling to identify useful biomarkers. Dr Price provided an impressive overview of progress in developing a personalized medicine approach to schizophrenia/bipolar disease treatment. Here, a proprietary computational approach, Homomatrix, based on principle component analysis, compared mRNA expression profiles from brain and blood samples analyzed with Affymetrix Chips. Four distinct schizophrenia and bipolar patient groups in three independent patient cohorts, brain 1 (n=64), brain 2 (n=90) and blood (n=115), were identified by gene clusters that were co-regulated. Interestingly, the subgroups were not linked to diagnosis (schizophrenia vs bipolar disease). In the brain studies, 400 to 600 genes differentiated between the groups and each subgroup has a statistically significant distinct molecular signature (p<0.001). In the blood studies, 220 genes differentiated between subgroups. The overlap between the three cohorts was good. Identical genes were identified in the two brain studies, while the overlap between brain/blood studies was 34/36, 57/59, 34/66 and 11/35 for a total of 130 co-regulated genes. A developed diagnostic blood test that used expression level of 28 genes to distinguish between subgroups in 32 member schizophrenia/bipolar patients had 78% sensitivity (ability to detect all members of a subgroup) and 94% specificity (ability to avoid assignment to wrong subgroup).

Curidium identified multiple drug targets and candidates. Some drug candidates that they acquired failed in phase II (n=2) or phase III (n=2) due to lack of efficacy in other diseases, and two others are nearing the end of patent life and are available on the market. Drugs and their former clinical phase are for subgroup A, CRD-105 (phase III); subgroup B, CRD-106 (phase III), CRD-107 (phase II), CRD-109 (previously launched); subgroup C, CRD-103 (previously launched), CRD-108 (phase II), and CRD-109 (previously launched); and subgroup D, CRD-108 (phase II). Obviously, the development of already tested drug candidates for treatment of specific subgroups will considerably shorten the time and reduce the expense of clinical development. Specific genes found in particular subgroups were PDE4B (subgroup A), NRG1, GrJk3 (subgroup B), PED3B, PDE4B, and NDEL1(subgroup C), and DISC1 and PED3B (subgroup D). In addition, analysis of the data by Pathway analysis (Ingenuity Systems) and comparison to the literature revealed links to cellular growth and proliferation, cell signaling, neurodevelopment and the immune response.

Dr Altar reported on results obtained by the company he was formerly associated, but which is now defunct, Psychiatric Genetics. Profiling samples with Affymetrix chips of frontal cortex and hippocampus of autopsied brain samples revealed small changes only when laser capture was used to limit the analysis to dentate granule neurons 1 and 2, and CA3 neurons 1 and 3. Many changes are similar to changes detected in muscle of the diabetic mouse. In both studies, decreases were found for the insulin responsive genes (eg, cytochrome c oxidase subunit VIIb; NADH dehydrogenase (ubiquinone)1 B22 subunit; cytochrome oxidase, subunit VIIa 3; ubiquinol cytochrome c reductase core protein 1; succinate dehydrogenase
cytochromome b subunit; ubiquinol cytochrome c reductase core protein 2; 1-4 to 1-6 glycan branching enzyme homolog; lactate dehydrogenase 2, B chain; pyruvate dehydrogenase E1 component - subunit; GLUT4, GDP dissociation inhibitor 1 and syntaxin 4); hexokinase II was differentially affected (ie, increased in schizophrenia and decreased in diabetic mouse muscle). These genes, plus well known signaling genes, insulin receptor B (IR-beta and phospho-IR-beta) and Akt (serine threonine protein kinase, total and phosphorylated active forms) decreased in the frontal cortex of patients with schizophrenia and were used to develop a screening system, called MPHTS, using SH-SYS5Y neuronal cells. In SH-SYS5Y cells, nerve process outgrowth is increased by insulin like growth factor (IGF-1) and insulin. In the MPHTS system, arrays of SH-SYS5Y cells are treated with potential drugs, then each culture is lysed and analyzed for mRNA changes in the schizophrenia signature of 14 genes (eg, TAP10).

Studies from Australia and the University of Pennsylvania document olfactory effects as early disease symptoms in schizophrenia, and are not related to severity of disease, neuroleptic use, or smoking. The olfactory receptor neurons are unusual in that neurogenesis takes place in adults. Nicola Cascella (Johns Hopkins University) reported on preliminary studies on mRNA profiling comparison using Affymetrix chips between biopsied olfactory neurons and immortalized lymphoplastoid cells from the same patient. Olfactory biopsies under local anesthetic involve taking four 2 mm pieces from each nostril. The biopsies and lymphoblasts shared upexpression of genes involved in cytoskeletal function as well as downregulation of AMP activated protein kinase anchor proteins (PRKAs). Future studies will develop laser capture of p75NGFR positive olfactory for comparative studies.

**Imaging markers**

Understanding of AD and other neurodegenerative diseases has progressed so that some subtypes are identified and some brain imaging markers appear to be developed that can be used in living patients. Franz Hefti (Avid Radiopharmaceuticals) described the development of pet imaging reagents based on the small molecule AV-1. Derivatives, exemplified by AV-19 (Bayer Schering Pharma), have high brain penetrance, high affinity and specificity for the amyloid beta peptide, no reported toxicity, and appear to image plaques in early AD. The radiopharmaceutical 11C-PIB (Pittsburgh compound B; University of Pittsburgh/Uppsala Imanet) is another amyloid deposit potential imaging reagent tested in individuals with mild cognitive deficits or putative early AD. It remains to be seen whether imaging results will correlate with disease progression. The half-lives for decay of 11C, 18F and 99mTc are 20 min, 2 h, and 6 h, respectively.

**Drug development**

**MEM-3454**

Stephen Murray (Memory Pharmaceuticals) reported on MEM-3454, a novel alpha 7-nicotinamide agonist. The compound is in phase II testing for AD and schizophrenia. Alpha 7-nicotinamide agonists mimic antipsychotics by increasing dopamine and acetylcholine in the medial prefrontal cortex and ventral hippocampus. MEM-3454 appears to reverse sensory gating deficits in the water maze test with young rats with an efficacy that is 30-times lower than levels associated with significant adverse event occurrences.
Issues besides behavior markers that need to be considered for pilot trials are proof-of-concept definition, go/no go decision points, a dose response, and they should be quick and inexpensive. The design of the schizophrenia trial includes: i) established diagnosis of schizophrenia (not first episode); ii) 40 individuals per arm assuming a relevant effect size of 0.5, and standard deviation similar to that in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE); iii) include patients on polypharmacy; iv) duration under 12 weeks (best at 4 to 6 weeks to minimize dropout); v) assessment uses a panel of tests (total duration 3 h) that include MATRICS, PANSS MADRES, UPSA-brief, PSP, Simpson-Angies, Barnes; and vi) usually, smoker exclusion.

**Neuroprotective peptide**

AL-108 (for intranasal administration) and AL-208 (for intravenous administration) deliver a neuroprotective peptide (amino acid sequence NAPVSIPQ) being tested for use in AD, mild cognitive impairment, and schizophrenia. Bruce Morimote (Allon Therapeutics) reported that AL-108 is the smallest active peptide of activity-dependent neuroprotective protein (ADNP), an approximately 1100 amino acid protein essential for brain development, learning, development, and response to injury. AL-108 crosses the blood-brain barrier, stabilizes brain microtubules, and restores axonal transport.

Nasal and intravenously administered AL-108 was tested in a 'state-of-the-art' triple fragile mutant mice exTg model. The nasal route potentially provides a direct route to the brain, although nasal administration of AL-108 leads to blood loading. A 3-month treatment led to a 20% reduction in beta amyloid levels, 70% reduction in Tau hyper-phosphorylation, and spatial and temporal memory improvements. Preclinical testing has involved intranasal and intravenous routes.

**AMPAKINEs**

AMPAKINEs, allosterically modulate AMPA-type glutamate receptors, facilitate long-term-potentiation (LTP), and improve rodent and non-human primate cognitive task performance. Mark Varny (Cortex Pharmaceuticals) reported that there are four AMPA-type receptors that combine to form tetramers (usually homomeric) that are responsible for fast excitatory synaptic transmission. AMPAKINEs (eg, CX-717) attenuate the rate of receptor deactivation, and, in animal models, increased motor performance and decreased fear conditions that appeared to be specific for AMPA-type glutamine receptors.

**Hypothalamic-pituitary-adrenal axis**

Maladapted stress response mediated by the hypothalamic-pituitary-adrenal (HPA) axis impairs the ability of the body to cope with infection, injury and environmental exposures. There is increasing evidence linking HPA axis dysfunction to psychiatric disease, including depression, anxiety, irritable bowel syndrome (IBS) and sleep disorders. The stress response is partially modulated by the neurohormones/neurotransmitters, corticotropin releasing factor (CRF; a 41 amino acid peptide modulating acute stress), and vasopressin (modulating moderate stress). These factors activate pituitary receptors and the HPA axis in the brain leading to increased vigilance, decreased feeding and sexual behavior, and in the periphery,
producing changes in blood pressure, metabolic patterns, and inflammation. Depressed patients have hypercortisolism, increased urinary free cortisol, increased adrenal gland volume, blunted CRH stimulated adrenocorticotropic hormone (ACTH) release, increased cortisol response to ACTH, and dexamethasone non-suppression. A number of CRH-1 and V1b antagonist are being testing in CNS, and the key question is whether drugs can be developed without side effects. The drugs under development by Organon and described by the company's Executive Director of Pharmacology, David Hill, include a CRH-1 antagonist, V1b receptor antagonist ORG-52186, and ORG-X (targeting the glucocorticol receptor). All these appear to have better efficacy than ORG-34517 and ORG-34850, which lack specificity when compared with mifepristone. Phase I studies of ORG-34517 showed that the compound was well tolerated, had no antidepressen effect and appeared useful as an adjunct treatment to decrease psychotic symptoms in psychotic major depression (PMD) patients.

Allosteric inhibitors of CRF1

Nicholas Lodge (Bristol-Myers Squibb) reported that a number of potent and selective allosteric inhibitors of the CRF1 receptor that are effective in animal of anxiety, depression and IBS models (ie, reduce plasma corticosteroids and defensive withdrawal) are proposed as therapies for these human conditions. A lead CRF1 inhibitor is pexacerfont (BMS-562086) and preclinical testing showed an anxiolysis effect was achieved with lower doses than that required to blunt a stress response.

Triple reuptake inhibitors

Triple reuptake inhibitors (TRIPs; aka broad spectrum antidepressants) are the focus of a new generation of potent antidepressants expected to have lower side effects, strong antidepressant effects, and to treat anhedonia (inability to experience pleasure). The goal of these drugs is to enhance the action of dopamine, serotonin and norepinephrine to treat depression, obesity, ADHD, substance abuse, premenstrual dysmorphic syndrome (PMDD), pain, anxiety, and cognitive disorders. Antidepressant drugs have evolved from tricyclic antidepressants (TCS, 1958), selective serotonin reuptake inhibitors (SSRIs, 1988), serotonin norepinephrine reuptake inhibitors (SNRIs, 1994), norepinephrine reuptake inhibitors (NRIs, 1997), and today, TRIPs. Now, approximately 75% of patients respond to SSRIs and it is hoped that TRIPs will increase the number of respondents, reduce relapse, and have a faster onset rate and fewer side effects (eg, sexual dysfunction, nausea and gastrointestinal effects - often linked to SSRIs).

Phil Skolnick of DOV Pharamceuticals reported that the inhibition concentrations (IC50 value in nM) for dopamine:serotonin:norepinephrin (D:S:N) for DOV-216303 (a mixture of the - and + racemers that make up the derivative compounds DOV-21947 and DOV-102677) are 78:14:20, 96:12:23 and 130:130:100, respectively. In comparison, the D:S:N values for SNRIs, duloxetine and venlafaxine are 420:3:3:17 and 2900:130:1201, respectively. No statistical difference was found in efficacy or in adverse effects in a randomized double blind phase II study of DOV-216303 (100 mg/day) versus citalopram (40 mg/day). The 2-week study used the HAM-D scale as the primary outcome measure with 67 subjects (inpatient or outpatient; major depressive disorder; HAM greater than or equal to 20, depressed mood >1, HAMA less than or equal to 15 decrease of >20% excluded, suicidal patients excluded, adequate washout from prior CNS medication); this study was not designed to detect
differences between the drugs. DOV-21947 was active in preclinical models of depression and significantly increased dopamine, serotonin and norepinephrine in the brain at doses that did not increase motor activity. A double-blind, placebo and active controlled phase II trial in depressed patients is to begin in 2007 for DOV-21947. Rat and mouse diet-induced (DI) obesity and toxicology studies in dogs and rabbits indicate that this compound may be a useful obesity treatment. Already approved TRIP anorectic agents, manzolin and sibutramine, have IC50 (nM) values of 29:160:3 and 943:298:5000 for D:S:N, respectively.

Aloke K Dutta (Wayne State University) reported on SNRI, NRI and TRIP activity of novel, recently synthesized, asymmetric tri- and di-substituted pyran derivatives. One compound, D-161 has IC50 (nM) values of 87:37:5 for D:R:N, respectively. Molecules were designed following Lipinsky's rules for making biologically active oral drugs. Studies in animal models of depression revealed that D-161 was more potent than the reference drug imipramine. There was potent antidepressant activity in the tail suspension test, and no stimulatory effect in the locomotion activities test. Molecules with triple uptake activity exhibited highest affinity for the norepinephrine transporter followed by potent to good activity at the both serotonin and dopamine transporters.

Summary

Overall, the meeting was forward looking with a good mix of presentations of the problems and progress in the development of biomarkers for CNS disease. Clear-cut progress has been made in developing cognitive biomarker tests, some molecular gene expression signature, drug signatures and an appreciation for the impact of novel pathways on disease presentation. It is quite clear that preclinical and clinical testing of potential CNS drugs requires, unlike other diseases, quantitative measures that accurately predict efficacy and side effects and recent progress has been made in this area. Progress on a number of drugs was discussed. However, it is also clear that the drug development pipeline has generally ignored the potential to impact CNS disease by interfering with, or reversing, linked environmentally mediated biological or biomolecular changes.

The website for this meeting can be found at http://www.almevents.com/conf_page.cfm?pt=&amp;amp;web_page_id=&amp;web_id=996&amp;web_id=5797.

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