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The conference on Psychiatric Drug Discovery and Development was organized by Strategic Research Institute, New York, NY and held at the Westin Princeton at Forrestal Village, Princeton, NJ. It was chaired by Paul McGonigle (Univ. of PA) and Darryle D. Schoepp (Eli Lilly and Co.) and consisted of 5 sessions with a total of 19 lectures, each of 35 to 45 minutes duration. The conference was attended by ca 70 scientists, mostly from major pharmaceutical companies.

Discovery and Development of Psychotherapeutics

The first lecturer was **William T. Carpenter** (Univ. of Maryland). According to him schizophrenia (SZ) is not a single disease entity. It is a syndrome that includes different diseases. One form of schizophrenia is characterized by deficit psychopathology, while another form has no deficit features. Cognitive pathology (impairment of attention, memory, thought processing and executive control) may be present without reality distortion and other symptoms. Antipsychotics affect psychosis, but not cognitive impairment in schizophrenic patients. The heterogeneity of SZ opens the opportunity for the development of new drugs to treat various symptoms. Experimental models are being developed to treat various aspects of SZ. Gestational insult is a risk factor for SZ. If pregnant rats are subjected to stress, increase in motor activity and in sensitivity to amphetamine can be detected in newborn rats as late as 35 or even 56 days after birth. Drugs can be tested for antagonism of these behavioral changes. Some of Carpenter's views were discussed in the article by B. Kirkpatrick et al. (*Arch Gen Psychiatry* 2001;58:165–171).

Paul McGonigle (Univ. of Pennsylvania) discussed neurogenesis as a target for potential antidepressant drugs. Atrophy and cell loss in the hippocampus and prefrontal cortex have been found in patients with depression. Stress can trigger episodes of depression. Neurogenesis can take place in the adult brain. It is enhanced by environment, learning,

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estrogens, caloric restriction and inhibited by opiates, metamphetamines, glucocorticoids, aging and stress. According to McGonigle, antidepressants block stress-induced inhibition of neurogenesis in hippocampal neurons. Neurogenesis in the dental gyrus can be increased by chronic treatment with tranylcypromine or fluoxetine. Risperidone also increases neurogenesis. Psychosocial stress in shrews decreases cell proliferation in dentate gyrus and this effect is antagonized by tianeptine. McGonigle suggested that antidepressants may be active in depression by restoring or enhancing neurogenesis. Brain-derived neurotrophic factor (BDNF) increases neurogenesis and prevents stress-induced neuronal atrophy in hippocampus. By infusion into the dental gyrus BDNF has an antidepressant effect in animals. Neurogenesis can be used to screen for novel antidepressants.

According to **Jeffrey Sprouse** (Pfizer) modulation of circadian rhythms is a new target for psychotherapeutics. The biological clock is a highly conserved function in the plant and animal kingdoms. Dysregulation of the clock occurs in various disorders of the central nervous system. Depression can be improved by phase shifting or sleep deprivation. Sleep disorders can be caused by disturbances of Circadian rhythms. The pharmacology of biological clock is complex, but substantia nigra neurons (SCN) play the central role. In addition to GABA, SCN neurons contain many neuropeptides. Their release is controlled by NPY, 5-HT, and other receptors. Rhythmic activity of SCN neurons is coordinated by a diffusible factor; other factor(s) may control the output to hypothalamus. A gut peptide (prokinectin 2) may conceivably control SCN output. Additional targets for regulation of clock may involve casein kinase 1 ϵ , 5-HT₇ and 5-HT_{5A} receptors.

Use of imaging in the development of psychotherapeutics was discussed by **Richard Hargreaves** (Merck & Co., West Point, PA, USA). Imaging allows detection of pharmacological effects of drugs within the living brain and is particularly useful during early clinical studies. At Merck imaging is incorporated into the discovery program and lead optimization. It includes: 1) neuroreceptor mapping with position emission tomography (PET), 2) metabolic mapping (glucose metabolism, blood flow etc.), 3) structural and functional studies using magnetic resonance imaging (MRI). Neuroreceptor mapping provides a unique bridge between laboratory receptor occupancy studies and clinical efficacy evaluation and helps in the interpretation of clinical findings. The use of PET in the imaging of substance P receptors (NK1) was described by Hargreaves [*J Clin Psychiatry* 2002;63(Suppl 11):18–24].

Genomics in the Discovery of Psychotherapeutics

The title of **John Reid's** (AstraZeneca) presentation was "Impact of Genetics on Psychiatric Drug Discovery." The search for antipsychotic drugs is rapidly expanding. There are 5 to 6 million schizophrenics worldwide. There is a substantial hereditary component in this disease. It may involve multiple genes, including recently discovered susceptibility genes. Genetics is likely to play an important role in the search for new antipsychotic drugs. AstraZeneca established collaboration with leading institutions involved in the search for genes responsible for schizophrenia and is conducting in-house research in this field. Reid assigns a central role in the pathogenesis of schizophrenia to glutamatergic transmission. Gene products may affect synaptic plasticity. Research goals in this area include identification of genes involved in synaptic formation and conductivity, their expression in key neurons, as well as the pattern of multiple gene defects. In this research

AstraZeneca collaborates with NPS Pharmaceuticals. Genomic approach permits the study of altered patterns of expression of genes that control synaptic connectivity.

Daniel R. Weinberger (NIMH, NIH) was the keynote speaker of the conference. The title of his presentation was “Genes to Targets: Dissecting Genetic Mechanisms of Psychosis.” Significant association of the following genes: COMT (22q), dysbindin (6p), G72 (13q), NRG-1 (8p), GRM-3 (7q) and DSCI (1q) with psychosis was confirmed at the NIMH. For the gene that encodes catecholamine-O-methyl transferase (COMT) functional polymorphism was found to affect prefrontal cortical function by modifying dopamine signaling and information processing. The current challenge is to understand how other genes increase the susceptibility to schizophrenia and how they relate to clinical disease. The association of COMT with prefrontal function was extensively studied. COMT knockout mice have increased levels of prefrontal dopamine and enhanced memory. COMT inhibition increases working memory. COMT gene impacts at the level of synaptic function. Prefrontal function and striatal dopamine activity appear to be inversely related. GRM3 gene is directly involved in glutamate signaling. High risk GRM3 (p26–27) allele impacts on glutamate levels. GRM3 appears to downregulate the glial transporter. Neuregulin 1 (NRG1) affects CNS development via specific signaling at EGF receptors. On the basis of the available information Weinberger constructed an emerging genetic architecture of schizophrenia that includes primary and modifying traits and interaction between prefrontal and hippocampal deficits.

Novel 5-HT and Dopamine Agonists and Antagonists

Smriti Iyengar (Eli Lilly & Co.) presented a preclinical profile of a selective 5-HT and norepinephrine (NE) reuptake inhibitor, duloxetine, and discussed its use in the treatment of depression and persistent pain. *In vitro*, in synaptosomes of rat cerebral cortex, duloxetine has been shown to inhibit 5-HT and NE uptake. Inhibition of 5-HT and NE reuptake has been also demonstrated *in vivo*.

Duloxetine

Duloxetine is also effective in experimental models of persistent pain, as well as in patients with diabetic neuropathic pain. Physical signs of pain are common in ca 40% of patients with depression. These physical signs are responsive to duloxetine, but not to SSRIs. Pain sensation is modulated in the spinal cord. Descending facilitatory as well as inhibitory pathways involve 5-HT. It was suggested that inhibition of the uptake of both neurotransmitters is needed for inhibition of persistent pain.

According to **Sharon Rosenzweig-Lipton** (Wyeth, Princeton, NJ, USA) 5HT_{2C} receptors represent a target for drugs affecting mood disorders. These G-protein- and phospholipase C-coupled receptors are widely distributed in the brain. They are largely absent in heart, aorta, blood vessels and endothelial cells. Potential therapeutic indications for 5-HT_{2C} agonists include obesity, depression, obsessive-compulsive disorder and schizophrenia. 5-HT_{2C}-knockout mice are obese, hyperphagic, have elevated insulin and leptin levels as well as impaired glucose utilization. Wyeth developed WAY-161503, a 5-HT_{2C} agonist with a K_i of 4 nM.

At 3 and 10 mg/kg i.p. WAY-161503 decreased food intake in normal and obese Zucker rats. At 1 and 3 mg/kg i.p. WAY-161503 decreased immobility in forced swim test in rats. At 0.1 and 0.3 mg/kg s.c. WAY-161503 decreased aggression in the rat resident-intruder model. At 1 or 2 mg/kg i.p. it decreased water intake in schedule-induced polydipsia. At 10 and 20 mg/kg i.p. WY-161503 reduced apomorphine-induced climbing/stereotypy. At 1 to 3 mg/kg i.p. WY-161503 reduced conditioned-avoidance responding in rats. The above listed and other results indicate that WY-161503 and possibly other 5-HT_{2C} agonists will be effective in the treatment of obesity depression, anxiety and schizophrenia.

Darryle D. Schoepp (Eli Lilly & Co.) discussed the role of mGluRs in anxiety and stress disorders. Glutamate is the major neurotransmitter in CNS. Modulation, rather than inhibition or stimulation, of glutamate neurotransmission is a desirable approach to the regulation of physiological effects of glutamate. There are at least 30 drug targets that are capable of modulating glutamate neurotransmission. Eight metabotropic glutamate receptors (mGlu1–mGlu8) were identified and cloned. mGlu receptors are located pre- as well as post-synaptically. Presynaptic release of glutamate is reduced by activation of mGlu₂, mGlu₄, mGlu₇ and mGlu₈ receptors and enhanced by activation of mGlu₇ receptors. Post-synaptically mGlu₂ and mGlu₃ receptor activation can modify neurotransmission at NMDA receptors. CNS diseases that involve inappropriate excitatory neurotransmission include epilepsy, neurodegenerative diseases, neuropathic pain, schizophrenia and cognition disturbances. Lilly's scientists rationally designed an mGlu_{2/3} receptor agonist, LY354740, which was expected to modulate glutamate neurotransmission pre- as well as post-synaptically.

LY354740 is a selective and potent agonist at animal and human mGlu2 and mGlu3 receptors. It suppresses glutamate-induced excitation in select synapses and is effective in animal models of anxiety and stress. Its pharmacological profile differs significantly from that of diazepam. The anxiolytic effects of LY354740 appear to be mediated via the hippocampus as well as via the amygdala. In hippocampal neurons it reduces stress-induced excitability, while in amygdala it increases neuronal activity of GABAergic cells, which tend to suppress stress. Clinical studies validated pharmacological findings. Its major clinical indication is generalized anxiety disorder (GAD). The additional indications for LY354740 include panic attacks, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD).

Kimberly E. Vanover (Acadia Pharmaceuticals) presented ACP-103, a 5-HT_{2A} receptor inverse agonist, a novel potential treatment for psychosis. It is currently in development for a very restricted indication, psychosis in Parkinson's disease. The K_i of ACP-103 for 5-HT_{2A} receptors is 0.4 nM; it is more selective for 5-HT_{2A} receptors than any other known antipsychotic. It has only weak affinity for 5-HT_{2C} receptors. At 1 mg/kg s.c. or at 3.0 mg/kg p.o. it inhibits MK-801-induced hyperactivity in mice. Unlike haloperidol ACP-103 does not produce catalepsy in mice. Its oral bioavailability in rats is greater than 43%. Its peak brain concentrations are reached at 2 h after oral administration. The drug is detectable in blood as late as 144 h after treatment. Phase 1 clinical study has been completed, and the drug is safe at 50 or 100 mg per day for 14 days. Acadia is looking for a partner for further development of ACP-103. The chemical structure of the drug has not been revealed.

Sam Kongsamut (Aventis) spoke about the discovery and development of dopamine D₃ antagonists for the treatment of schizophrenia. D₃ receptors represent a reasonable target for antipsychotic drugs. They are concentrated in the mesolimbic brain region. There is a genetic association between the D₃ receptor gene and schizophrenia. Behavioral abnormalities in animal models of schizophrenia are attenuated by the blockade of dopamine D₃ receptors. AVE5997, a D₃ antagonist, and AVE1734, a D₃ partial agonist, were identified at Aventis as promising compounds and evaluated in functional assays. AVE1734 was active as an antagonist in the adenylyl cyclase assay (IC_{50} = 8.4 μ M) and in MAPKinase assay (IC_{50} = 79 nM). Its EC_{50} for partial agonist activity in MAPKinase assay was 10 nM. In mitogenesis assay its EC_{50} as a partial agonist was 3 nM. AVE1734 antagonized MK-801-induced hyperactivity at 0.1 mg/kg s.c. AVE5997 had no agonist activity in any of the assays used; it had antagonist activity in the adenylyl cyclase assay with an IC_{50} of 33 μ M and in MAPKinase assay with an IC_{50} of 30 nM. It antagonized MK-801-induced hyperactivity with an ED_{50} of 0.1 mg/kg p.o. The chemical structures of the two compounds were not revealed.

Andreas Braun (Sequenom) outlined a genome association approach used by Sequenom to find new leads for psychotherapeutics. The initial genomics discovery (genome scan) is followed by proximity SNP analysis, replication study, resequencing, secondary phenotype analysis and biological assessment. Sequenom identified specific novel targets for schizophrenia, Alzheimer's, bipolar disorder, and depression. They are currently looking for collaborators to develop or to license these leads.

Neuropeptides

Karen A. Maubach (Merck & Co., West Point, PA, USA) discussed the antidepressant and anxiolytic effects of substance P antagonists. It has been established that deletion, or blockade of neurokinin 1 receptors (NK1), leads to anxiolytic-like and antidepressant effects in behavioral assays. Psychotherapeutic effect of Substance P Antagonists (SPAs) may also be mediated by a direct blockade of NK1 receptors in the amygdala and/or associated output pathways. SPAs promote synaptic remodeling and neurogenesis and regulate neuronal functions of norepinephrine (NE) and 5-HT. The pharmacological and clinical profiles of SPAs are distinct from those of currently used antidepressants. SPAs caused burst of firing in locus coeruleus neurons, no desensitization of α -adrenoceptors and no increase in extracellular NE efflux. Merck is developing its own SPAs, L-760735 (structure not revealed). At 3 mg/kg/day L-760735 causes burst firing in locus caeruleus NE neurons in guinea pigs and alters firing characteristics of dorsal raphe 5-HT neurons. SPAs represent a new and clinically validated approach to the therapy of depression.

Tom P. Blackburn (Synaptic, Corp., Paramus, NJ, USA, now Lundbeck & Co.) discussed the pharmacology of SNAP 7941, a melanin-concentrating hormone (MCH) receptor antagonist. MCH antagonists are known to be useful in the treatment of obesity. They were recently shown to be effective as antidepressants and anxiolytics as well.

SNAP 7941

SNAP 7941 is a highly selective antagonist of human MCH1 receptors; its K_i is 0.08 nM. At 1 or 10 mg/kg i.p. SNAP 7941 antagonized MCH-stimulated food intake in rats. At 3 to 30 mg/kg p.o. it decreased immobility in the forced swim test in mice or rats. It had anxiolytic effects in rat social interaction, the maternal separation vocalization test, and the rat Vogel conflict test. It increased the number of spontaneously active dopamine neurons in A10, but not in A9 area, of the brain. These findings support possible usefulness of SNAP 7941 in the treatment of anxiety and depression.

Guy Griebel (Sanofi-Synthelabo) spoke about vasopressin V1b receptors as a therapeutic target in stress-related disorders. V1b receptors are localized in brain areas known

to modulate anxiety behavior in rats. Immobilization stress increases V1b receptor mRNA. SSR149415 is a highly selective ligand for rat and human V1b receptors.

SSR149415

SSR149415 inhibited arginine vasopressin (AVP)-induced calcium increase in CHO cells ($IC_{50} = 3.8$ nM). At 30 mg/kg p.o. SSR149415 had a weak anxiolytic effect in the elevated plus-maze test in rats. At 3 mg/kg i.p. it increased the number of punished responses in the Vogel conflict test. At 0.3 mg/kg p.o. and higher doses SSR149415 was effective in the elevated plus-maze test in mice following social defeat. At 10 or 30 mg/kg p.o. it reduced offensive aggression in hamsters. In forced swim test in rats SSR149415 reduced immobility time at 10 or 30 mg/kg p.o. By repeated administration (10 mg/kg/day p.o. for 39 days) the drug reduced stress-induced degradation of the physical state in mice and prevented decrease in neurogenesis in the hippocampus of mice. On the basis of the above listed and other tests Griebel concluded that SSR149415 and other VP1 antagonists could be useful in the treatment of depression and disorders caused by traumatic stress.

Target Identification and Validation

Ewa Malatynska (Johnson and Johnson) discussed dominant and submissive behavior in rats as models for antimanic and antidepressant drug testing. Submissiveness is thought to be a model for depression, while dominance is assumed to be a model for mania. Food-restricted rats are randomly paired and allowed to compete for food. During a two week period submissive and dominant behaviors (SDBs) develop in 44% of animals. The SDBs remain stable for at least 5 weeks. The submissive behavior is sensitive to standard antidepressants and dominant behavior is sensitive to lithium.

C. Anthony Altar [Research Psychiatric Genomics (PRG), Gaithersburg, MD, USA] spoke about genomic approaches to psychiatric target identification, validation and drug discovery. The mission of Research Psychiatric Genomics is to be the first company to use gene pathway analysis to discover small molecules to treat the causes of mental illness. Genes are viewed as keys to understanding psychiatric diseases and drug action. PRG is

using microarray analysis of dissected brain tissue from patients and normal controls to establish “disease signature.” Analysis of brains from animals treated with drugs is used to establish “drug signature.” Convergence of genes from disease and drug signatures permits identification of gene targets for drug discovery. Numerous leads for the treatment of bipolar disorder and for mood stabilization have been identified.

The title of **Thomas H. Lanthorn's** (Lexicon Genetics, Inc.) presentation was “What is Right with our Mice.” The presentation covered not only knockout mice, but also the discovery of LG617, a protein associated with Alzheimer's disease and of small molecule antagonists of this protein. Lexicon raises their own mice and produces knockouts for drug discovery programs. In addition, Lexicon established high throughput behavioral assays that include a pre-pulse inhibition test to detect antipsychotic activity, open-field exploratory activity, stress-induced hypothermia for depression, trace-fear conditioning to detect cognitive effects, Yaksch's automated nociceptive analysis for neuropathic pain, etc. As an example of Lexicon's research projects Lanthorn described the discovery of LG617, a membrane protein associated with Alzheimer's disease. It is selectively expressed in the brain, primarily in glutamatergic neurons. Lexicon screened ca 200,000 compounds and found LG617 antagonists that have therapeutic potential. The chemical structures of LG617 or its antagonists were not disclosed.

Holger Heimisch (Axaron Bioscience AG, Heidelberg, Germany) discussed cell type-specific expression profiling and its application for the development of drugs. Axaron assists its customers in the development of novel therapeutics for neurological disorders using functional genomics and proteomics. It is located on the campus of the University of Heidelberg. Originally Axaron was a joint venture of BASF and Lynx; it has been independent since 2001. Axaron's proprietary methodology for cell-type specific transcription profiling is called AXAMINER. It labels cell type of interest, dissects them automatically, amplifies mRNA by several orders of magnitude and profiles expression by microarray technology. Axaminer is extremely sensitive; it operates reproducibly on a picogram scale. It provides immunostaining without RNA degradation. The customers are expected to identify cell types of interest and to provide marker proteins.