SETTING PRIORITIES FOR PHENOTYPING THE MOUSE NERVOUS SYSTEM AND BEHAVIOR

Summary by

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BACKGROUND

The National Institute of Mental Health (NIMH) convened a distinguished group of national and international researchers for the purpose of establishing priorities for phenotyping the mouse nervous system and behavior. Approximately 50 scientists met for two days in Warrenton, Virginia in June 2000 to discuss the following topics: strategies for implementing reliable and high-throughput assays to characterize inbred strains within multiple phenotypic domains of nervous system function and complex behavior; development of batteries of phenotyping assays to maximize cost-benefit ratios, breadth of coverage and detection of subtle phenotypic alterations in the nervous system function and complex behavior of mutants produced by random mutagenesis; construction of a public database from which comprehensive phenotypic information on both inbred strains and mutants would be widely available to the neuroscience community; and coordination of these activities with those being accomplished under ongoing efforts by the National Institutes of Health (NIH) and the Jackson Laboratory to establish baseline phenotypic data on commonly used inbred strains.

The goal was to enable and facilitate research by the entire community of neuroscience researchers who use the laboratory mouse as a tool for understanding the biology of the mammalian nervous system and complex behavior. Recommendations for funding included construction and curation of a comprehensive database and phenotyping of reference inbred strains and mutants in four phenotypic domains: (1) neural and sensory function; (2) complex behavior; (3) pharmacologic response; and (4) imaging and electrophysiology. These data will be used to establish a comprehensive catalogue of genetic mutations and resulting aberrant mouse phenotypes, comparable to how McKusick's *Mendelian Inheritance in Man* catalogues single gene defects and associated human disease phenotypes. The recommendations are in the form of estimated direct costs for the first year and length of effort in years. Below is a summary of these recommendations.

INBRED STRAINS

Inbred mouse strains represent unique genotypes accessed as homogeneous populations. Systematic collection of baseline data from a standard set of inbred strains will provide critical information for the full interpretation of abnormalities in nervous system function and complex behavior observed in genetically altered mice, and selection of background strains for mutagenesis and other genetic experiments.

A. High-Priority Strains for Baseline Characterization

An array of nine inbred strains have already been identified as high priority for the Jackson Laboratory's Phenome Project (K. Paigen and J.T. Eppig: A mouse phenome project. *Mammalian Genome* 2000;11:715-717), a community-wide effort to establish baseline data for multiple basic phenotypes (blood pressure, heart rate, body weight, bone density, histopathology, urinalysis, hematology, clinical chemistry, sensory function, and behavioral and cognitive assessments). These nine strains include 129/SvImJ, A/J, BALB/cJ, BTBR, C3H/HeJ, C57BL/6J, CAST/Ei, DBA/2J, and FVB/NJ. It is recommended that comprehensive baseline data on nervous system function and complex behavior be collected on these nine inbred strains.

B. Other Strains

It is recommended that baseline data be collected on additional strains available commercially from multiple suppliers (e.g., Jackson Lab, Taconic, Charles River, etc.). It is also recommended to phenotype important F1, F2, and F3 hybrids, selected outbred (CD1, Swiss Webster, NIH Black Swiss) lines, and wild type strains.

I. PHENOTYPING NEURAL AND SENSORY FUNCTION
TOTAL DIRECT COST FOR FIRST YEAR: $1.5 M – DURATION: 4 YEARS

A. Phenotypic Domains

Full understanding of abnormal behavioral and nervous system phenotypes requires detailed characterization on each of the four major sensory modalities of vision, hearing, taste and olfaction, as well as balance, nociception, proprioception, and thermal regulation. One or two non-invasive high-throughput assays for each major sensory domain are feasible, e.g., vision - optikinetic nystagmus, slit lamp ophthalmoscopy; hearing - acoustic startle at several frequencies/amplitudes, pre-pulse inhibition of acoustic startle; taste - two-bottle choice taste preference; olfaction - response to odor.

B. High-Throughput Phenotyping Battery

A battery of 12 high-throughput screens is recommended. An equivalent number of lower throughput and/or invasive secondary/tertiary assays were discussed for each domain as being essential to further characterize a mutant or strain. Examples of secondary screens include: vision - ERG, IOP, morphology; hearing - ABR, DPOE, morphology; taste - additional compounds, lickometer; and olfactory - morphology. Assays for each modality are at a different state technically. Some have primary and secondary screens that are ready now (e.g. acoustic startle, two-bottle choice) and some still require development (e.g., olfaction). Some of this assay development is already underway and being supported by NIH in projects funded under RFA MH-99-006, "Phenotyping the Mouse Nervous System and Behavior." It is recommended to phenotype high-priority strains (129/SvImJ, A/J, BALB/cJ, BTBR, C3H/HeJ, C57BL/6J, CAST/Ei, DBA/2J, and FVB/NJ) and other commonly used inbred strains from multiple vendors.

C. Data Collection

State-of-the-art phenotyping of sensory domains in a reliable fashion is critical. In order to establish that phenotypic assessment is done in a highly reproducible way, it is recommended that different animals be tested on the same assay in two independent laboratories. Reliability studies will be conducted to clearly establish reliability across laboratories. A network of 6-10 laboratories, with one laboratory providing coordination and administrative oversight, is recommended to provide comprehensive assessment of multiple domains and to permit establishment of inter-laboratory reliability. The estimated direct cost is $1.5 M in each of four years.

II. PHENOTYPING COMPLEX BEHAVIOR
TOTAL DIRECT COST FOR FIRST YEAR: $1.8 M – DURATION: 4 YEARS

Full understanding of abnormal behavioral phenotypes requires baseline data from inbred strains, as well as detailed characterization in genetically altered mice.

A. Phenotypic Domains

It is recommended to apply high-throughput assays and characterize multiple domains of complex behavior: circadian rhythms and sleep; fear, anxiety, and emotionality; social interaction, including aggression; reproductive and parental behaviors; learning, memory, and attention; sensorimotor gating; motor and exploratory behavior; and feeding behavior.

B. High-Throughput Phenotyping Battery

It is recommended to develop and apply a battery of 10-12 high-throughput behavioral assays. Several new assays for use in this effort are being developed in projects funded by RFA MH-99-006, “Phenotyping the Mouse Nervous System and Behavior.” It is recommended to phenotype high-priority strains (129/SvImJ, A/J, BALB/cJ, BTBR, C3H/HeJ, C57BL/6J, CAST/Ei, DBA/2J, and FVB/NJ) and other commonly used inbred strains from multiple vendors (e.g., C57BL/6NCrl). In addition, the strain comparison should include 1-2 outbred strains of mice (CD-1 or Black Swiss).

C. Data Collection

State-of-the-art phenotyping of behavioral domains in a reliable fashion is critical. Phenotyping experts need to establish and utilize the assays for each behavioral domain to characterize animals. In order to establish that phenotypic assessment is done in a highly reproducible fashion, it is recommended that different animals be tested on the same assay in two or three independent laboratories. Reliability studies will be conducted to clearly establish reliability across laboratories. A node of 5-10 laboratories, with one laboratory providing coordination and administrative oversight, is recommended to provide comprehensive assessment of multiple domains and to permit establishment of inter-laboratory reliability. The estimated direct cost is $1.2 M in each of four years.

D. Development of New Behavioral Paradigms

There are still numerous human behavioral disorders that are poorly modeled in the mouse. These include, but are not limited to, models of behavioral despair, compulsive

behavior, attention, and social withdrawal. In addition, aspects of many behavioral abnormalities associated with neurobehavioral disorders including schizophrenia, bipolar disorder, autism, attention deficit hyperactivity disorder, and depression are currently modeled poorly. It is recommended that a high priority be given to the development of innovative behavioral assays in these areas. The estimated direct cost is $500,000 (support of 10 applications) in each of two years.

E. Training

There is an increasing interest and need for training in the behavioral analysis of mutant mice. The few existing courses are extremely popular and cannot accommodate the interested applicants on a yearly basis. It is recommended that new courses and workshops on the assessment of multiple behavioral domains in inbred strains and mutant mice be implemented. The estimated direct cost is $100,000 in each of four years.

III. PHARMACOLOGIC RESPONSE
TOTAL DIRECT COST FOR FIRST YEAR: $1.7 M – DURATION: 4 YEARS

Characterization of the effect of psychoactive substances on the nervous system and complex behavior of inbred strains and genetically altered mice is critical to the long-term goal of identifying novel drug targets for the treatment of neurobehavioral disorders.

A. Baseline Drug Response

Establishment of baseline pharmacologic data on administration, delivery, metabolism, and excretion is critical. In addition, it is recommended to establish high throughput assays to evaluate the impact of genetic manipulations on responses to drugs of abuse and psychotherapeutic compounds. To properly assess pharmacological responses, baseline behavioral responses need to be obtained prior to drug administration. In addition to behavioral studies, it is recommended to employ *in vitro* methods to further characterize genetic influences on pharmacological responses. For example, strain effects on receptor densities could be determined by radioligand binding procedures. Autoradiographic, Western blot, and second messenger assays also may be used to localize drug action in the brain and study function by elucidating signal transduction pathways.

B. Identification of Drugs

While many drugs may be studied, it is recommended to focus on those with varying mechanisms of action that produce robust behavioral effects in assays suitable for high throughput phenotyping. Such drugs of abuse include: alcohol, amphetamine, cocaine, phencyclidine, MDMA, and morphine. Several of these agents (e.g., phencyclidine, amphetamine, MDMA) are capable of inducing psychopathology that mimics particular features of neurobehavioral disorders. Genetic influences on these drug responses may be relevant to characterizing the genetic bases of both substance abuse and other neurobehavioral disorders. It is also recommended to choose psychotherapeutic drugs that are in common use for the treatment of major neurobehavioral disorders. These include: depression – paroxetine, desipramine; psychotic states – haloperidol, clozapine; anxiety states – midazolam, â-carboline; and Alzheimer's disease/dementia - scopolamine. It is recommended that several other compounds be studied, but the

absence of robust behavioral effects in current assays suitable for high-throughput phenotyping leads to a recommendation that they be assigned a lower priority. These include several drugs of abuse (LSD, nicotine, THC) and psychotherapeutic agents (nisoxetine, phenelzine, lithium, valproate, buspirone, fenfluramine). Development of robust, high-throughput assays for these drugs is recommended, at a cost of $500,000 in direct costs in the first year, for a period of two years.

C. High-Throughput Assays of Pharmacologic Response

A list of pharmacologic responses suitable to high throughput testing include: alcohol - locomotion/exploration, baseline startle amplitude; amphetamine - locomotion/ exploration, prepulse inhibition of startle (PPI); cocaine -locomotion/exploration, PPI; PCP - locomotion/exploration, PPI; morphine -locomotion/exploration, hot plate test; MDMA - locomotion/exploration; desipramine - forced swim test; paroxetine – tail suspension test; haloperidol - locomotion/exploration, catalepsy, temperature, PPI; clozapine - locomotion/exploration, temperature, PPI; midazolam - thigmotaxis in open field; â-carboline - thigmotaxis in open field; and scopolamine - locomotion/exploration. It is recommended to phenotype high-priority strains (129/SvImJ, A/J, BALB/cJ, BTBR, C3H/HeJ, C57BL/6J, CAST/Ei, DBA/2J, and FVB/NJ) and other commonly used inbred strains from multiple vendors (e.g., AKR).

D. Data Collection

It is recommended that dose-response data should be collected for high-priority inbred strains, with a minimum of three drug doses (plus vehicle). Pharmacokinetic data should be collected for each drug, and information provided regarding the p450 isozyme profile of each strain. It is also recommended that drug effects on body temperature be assessed, and that samples be taken for assays of blood chemistry and hormone levels. For high throughput phenotyping, it is recommended that each animal be treated with a single dose at the ED50 determined for that inbred strain or the appropriate background strain, and that individual assays should be run consistently on both male and female mice and at the same time of day to minimize variability attributable to diurnal influences on drug response. To minimize order effects, it is critical to perform state-of-the-art phenotyping of pharmacologic response in multiple laboratories. The assays described above can be performed across approximately five laboratories. In order to establish that phenotypic assessment is done in a highly reproducible fashion, it is recommended that inbred strains be tested on the same assay in two independent laboratories. Studies will be conducted to clearly establish reliability across laboratories. A network of 6-10 laboratories, with one laboratory providing coordination and administrative oversight, is recommended to provide comprehensive assessment of multiple domains and to permit establishment of inter-laboratory reliability. The estimated direct cost is $1.2 M in each of four years.

IV. IMAGING AND ELECTROPHYSIOLOGY
TOTAL DIRECT COST FOR FIRST YEAR: $1.55 M – DURATION: 4 YEARS

Molecular and structural neuroanatomic measurements are critical aspects to understanding the organization and function of the mammalian nervous system. There is a major need to enhance communication between the neuroimaging and mouse communities in the form of workshops/symposia to define promising new tools for screening assays. The estimated cost is $50,000 in the first year. For highly cost

effective imaging analyses of the nervous system, conventional light/fluorescence microscopic histopathology of inbred strains and mutants is recommended to systematically generate high-resolution neuroanatomic images. The estimated direct cost is $500,000 in each of four years. This work can be complemented with other high-throughput histologic measures that map regional brain metabolic activity, such as 2DG autoradiography. It is also recommended to characterize inbred strains and mutant mice at a secondary screen level with high-throughput differential screening with molecular and anatomical imaging techniques, e.g., assembly line microPET, micro-ultrasound, microCT, and microMRI. There is a high priority recommendation to adapt clinical electrophysiological techniques to characterize inbred strains and mutant mice. These methods include multi-electrode EEG, ERG, ECG, VER, ABR, DPOAE, SSER, and EMG. A network of 3-5 laboratories utilizing very high-resolution machines, with one laboratory providing coordination and administrative oversight, is recommended to provide comprehensive assessment of both nervous system structure and molecular function with multiple imaging technologies. One or more of these laboratories will also conduct electrophysiological studies. It is recommended to phenotype high-priority strains (129/SvImJ, A/J, BALB/cJ, BTBR, C3H/HeJ, C57BL/6J, CAST/Ei, DBA/2J, and FVB/NJ) and other commonly used inbred strains from multiple vendors. The estimated direct cost is $1 M in each of four years.

V. BIOINFORMATICS AND DATABASES
TOTAL DIRECT COST FOR FIRST YEAR: $1.35 M – DURATION: 4 YEARS

A significant amount of diverse phenotypic information will be generated that ultimately will facilitate research on the biological bases of nervous system function and complex behavior. Construction of a publicly available database of phenotypic data on inbred strains and mutants is a high priority for the research community. The difficulty of constructing a comprehensive phenotypic database is more complex than existing sequence-based genome databases. The current requirements and specifications of such a database are not well defined and do not adequately address prioritization of information to be included. Prior to developing a database and associated bioinformatics tools, it is strongly recommended to conduct a requirements analysis, at an anticipated cost of $100,000 over a six-month period in the first year. This method is commonly used in industry for gathering information regarding targeted users, information to be included in the database, which biological databases with which to link, and required retrieval tools employed across multiple databases that would be serve users. The information gathered from the requirements analysis will then be used to develop appropriate recommendations and a cost analysis for the construction of a comprehensive database and the development of highly efficient retrieval algorithms. Based on successful models used in industry, a budget of 15% – 20% of the total direct project costs is anticipated to provide adequate bioinformatics support and database construction and curation. It is strongly recommended to link such a database with other important databases of biologic information (e.g., genetic sequence, proteomics) relevant to mammalian biology and with comparable databases for other model systems (e.g., *Drosophila, C. Elegans*). Finally, there was a strong recommendation to development ways in which to support and maintain such databases in future years. The estimated direct cost for bioinformatics support, database construction, and curation is $1.25 M in each of four years.

FISCAL OVERVIEW
(October 23, 2000)

I. PHENOTYPING NEURAL AND SENSORY FUNCTION	**$1.5 M**	
High-throughput phenotyping of inbred strains, mutants	$1.5 M	4 yr
II. PHENOTYPING COMPLEX BEHAVIOR	**$1.8 M**	
High-throughput phenotyping of inbred strains, mutants	$1.2 M	4 yr
Development of new behavioral paradigms	$0.5 M	2 yr
Training	$0.1 M	4 yr
III. PHARMACOLOGIC RESPONSE	**$1.7 M**	
High-throughput phenotyping of inbred strains, mutants	$1.2 M	4 yr
Development of robust, high-throughput assays for LSD, nicotine, THC, nisoxetine, phenelzine, lithium valproate, buspirone, fenfluramine)	$0.5 M	2 yr
IV. IMAGING AND ELECTROPHYSIOLOGY	**$1.55 M**	
Workshops/symposia to develop new tools	$0.05 M	1 yr
Systematic histopathological studies of the nervous system	$0.5 M	4 yr
High-throughput phenotyping of inbred strains, mutants	$1.0 M	4 yr
V. BIOINFORMATICS AND DATABASES	**$1.35 M**	
Requirements analysis	$0.1 M	0.5 yr
Database construction and curation; development of search engines and other algorithms	$1.25 M	4 yr
TOTAL	**$7.9 M**	

BREAKOUT GROUP: Neural and Sensory Function
Wayne Frankel, Chair

1. How can the development of general, non-technologically demanding assays to characterize defects in axonal guidance, neuronal migration and synapse formation be facilitated?

2. What are the priority levels (high, medium, or low) and cost/benefit ratios for assays to be included in testing batteries, such that there are no more than 10 high priority assays?

3. Is high-throughput screening practical, and for which phenotypes?

4. Can batteries of assays be constructed such that order effects will not distort performance on subsequent assays?

5. How can the reliability, efficiency, and validity of such batteries be objectively monitored and quantified across multiple labs?

The group focused on phenotyping sensory systems and discussed in detail each of four major sensory modalities, vision, hearing, taste and olfaction. We set preliminary priorities for each modality based on what our panel members thought was needed and what is presently desired in each area and what is presently possible for high-throughput (e.g. mutagenesis primary screens) versus modest or low throughput (e.g. QTL mapping, secondary screens and strain surveys). Additional sensory modalities (nociception, proprioception, thermal regulation, somatosensory and vestibular function) were thought important but their feasibility was not discussed in detail because relevant expertise was not present in the group. Tentative recommendations on these modalities have been derived from subsequent discussion held outside of the breakout groups and thus are appended to the end of this report. We also discussed several general molecular tools necessary to enhance analysis of mutants. The following conclusions were drawn:

1. Assessment of vision, hearing, taste/olfaction, balance, nociception, proprioception, thermal regulation and somatosensory are all important to include in mouse phenotyping centers because a) there is a desire from researchers in each area to characterize more genes and variants in each, and b) most are essential for meaningful understanding of "real" behavioral mutants, i.e. to exclude confounding effects.

Specifically, between 1-2 non-invasive high-throughput assays for each sensory domain were discussed as feasible/desired, e.g. 2 for vision (e.g. optokinetic nystagmus or visual cliff, slit lamp ophthalmoscopy), 1-2 for hearing (e.g. acoustic startle at several frequencies/amplitudes, PPI of acoustic startle), 1 for taste (e.g., two-bottle choice taste preference) 1 for olfaction (e.g. reflexive respiratory changes in response to odor). Terminal high throughput assays are feasible in some easily dissected systems (e.g., ocular traits, histology analysis of cryostat sectioned material). Ideally, each screen would be refined to provide quantitative or semi-quantitative results without loss of throughput. Thus, including the domains not discussed specifically, approximately 12

high throughput screens would be required total. A few of these assays can be piggybacked quite easily onto each other, yielding effectively 10-15 assays specific to sensory systems.

An equivalent number of lower throughput and/or invasive secondary/tertiary assays were discussed for each domain as being essential to further characterize a mutant or strain. Examples were for vision (ERG, IOP, detailed retinal histology), hearing (ABR, DPOE, cochlear morphology), taste (additional compounds, lickometer, gustometer) and olfactory (odorant threshold sensitivity, odorant quality perception).

2. Assays for each modality are at a different state technically. Some have primary and secondary screens that are ready now (e.g., acoustic startle, two-bottle choice) and some have primary screens now under development, while their secondary screens are well in hand (e.g. olfaction). Some of this development is already underway (e.g., through the phenotyping RFA MH-99-006).

3. The communities for each modality come with a different set of goals and values when it comes to screening for and characterizing mutants. Thus, for example, vision researchers are more interested in cellular and physiological screens for specific cellular defects or partial impairment (such as loss of acuity or progressive impairments) and are less interested in variants that cause yes/no blindness. However, depending upon further assay development and refinement, severe visual impairment at late timepoints may provide a useful primary screen for identifying these more refined classes of greater interest. In contrast, researchers studying other modalities (e.g. taste) presently have few mutants to work with. Regardless of the state-of-the-art, those representing all modalities are intensely interested in gene discovery and strain characterization.

4. Several general tools to facilitate the analysis of neurosensory variants in strains and mutants were discussed. The development of 'reporter' strains for facilitating the tracing of neuronal circuits in a mutant would be quite desirable. The concept of multiplexed molecular markers for phenotyping was also discussed (for example, analysis of cell type-specific RNA or epitope markers in brain homogenates as a prescreen for anatomical or fate specification mutants). Each of these endeavors would be organized by phenotypic domain such that those with relevant system expertise (not necessarily the phenotyping centers alone) would develop appropriate reference sets of markers or reporter strains would best represent important deviations to each system and complement other phenotyping efforts.

Recommendation: Assay development and implementation would be done in phenotyping "Centers for Excellence" for each sensory domain. These would ideally consist of one or two satellite labs with expertise in given areas, in collaboration with a larger center or centers, (e.g., a mutagenesis facility which collaborates with multiple satellites) and in consultation with the broader community for each modality or domain. These collaborations would make it possible to assess reliability in > 1 lab and also to scale-up for mutation screens. The average cost per domain per year would be about $375K x 4 domain clusters (e.g. vision, hearing/balance, taste/olfaction, somatosensory/ociception/proprioception/thermal) = $1.5 M direct costs per year. This is based on a slightly larger than average R01 type operation for each, plus allowing for subcontract and associated costs (e.g. subcontract indirect costs). To make these centers truly useful, however, a commitment to investigator-initiated follow-up

research is essential. We would imagine that 2-3 labs would be interested in future following-up on mutants characterized in each modality (18-27 projects, average of 22 x $150K= $3.3M direct costs per year). These could use (small) R01, RO3 or competitive supplement mechanisms. This strategy is intended to encourage all grantees of participating Institutes to take maximum advantage of this resource and thereby inform and refine continuing efforts within centers. A recommendation for an additional modality (nociception) was also made. In response to a dinnertime query, Dr. Richard Paylor commented that tail flick and hot plate assays for pain sensation are sufficiently rapid and simple for high-throughput screening.

BREAKOUT GROUP: Complex Behavior
Jeanne Wehner, Chair

1. What phenotypes can be examined with existing paradigms, and what new ones need to be considered, in order to better model human behavioral disorders?

2. What are the priority levels (high, medium, or low) and cost/benefit ratios for assays to be included in testing batteries, such that there are no more than 10 high priority assays?

3. Is high-throughput screening practical, and for which phenotypes?

4. Can batteries of assays be constructed such that order effects will not distort performance on subsequent assays?

5. How can the reliability, efficiency, and validity of such batteries be objectively monitored and quantified across multiple labs?

Three basic recommendations are being made:

1. To establish an inbred strain data base for complex phenotypes and standardization of assays.

2. To spearhead an effort for new behavioral paradigm development in the mouse.

3. To facilitate training of scientists for the examination of complex behavioral traits via courses and workshops.

Rationale and proposed structure for recommendations:

1. **To establish an inbred strain data base for complex phenotypes and standardization of assays**

The need for a database is multidimensional:

1. Provide important information for ENU mutagenesis projects.
2. Provide information for selection of background strains for gene targeted strategies.
3. Provide information for selection of strains for QTL analyses.
4. To perform correlative analyses with the goal of applying information to selection of behaviors for secondary screens in ENU mutagenesis projects.
5. To interface with gene expression analyses between strains and analyses of behaviorally induced changes in gene expression.

Behavioral Domains for Analyses

Circadian behavior and sleep
Fear, anxiety, and emotionality
Social interactions and aggression
Reproductive and parental behaviors
Learning and memory, and attention
Sensorimotor gating
Motor and exploratory behavior
Feeding behavior

Structure of the Programs

A primary objective is to standardize behavioral assays to allow broader utilization by the scientific community in future gene discovery and characterization of mutants.

Proposed Standardization Plan

1. Standardization will require coordinated efforts in 2-3 labs for each behavioral assay. Clustering of behavioral domains is recommended for traits commonly evaluated in the same lab.
2. Development and optimization of protocols that are made available to the scientific community.
3. It would be advantageous to analyze 10-15 strains which should include commonly used inbred strains from multiple vendors (e.g., C57BL/6J and C57BL/6NCrl). In addition, the strain comparison should include 1-2 outbred strains of mice (CD-1 or Black Swiss).

Funding Mechanism

We recommend that these projects be supported as a multi-investigator contract coordinated by a central steering committee. It is estimated that the initial strain database would require two years of work. Once the behaviors are established, an additional two years would be used to evaluate various types of mutants including those derived using gene-targeting technology and random mutagenesis (chemical and insertional). We estimate the direct cost to be approximately $1.2 million per year for 4 years.

2. **To spearhead an effort for new behavioral paradigm development in the mouse**

There are still numerous human behavioral disorders that are poorly modeled in the mouse. These include, but are not limited to, models of behavioral despair, compulsive behavior, attention, and social withdrawal (interaction). In addition, aspects of many behavioral abnormalities associated with neurobehavioral disorders including schizophrenia, bipolar disorder, and depression are currently modeled poorly. We recommend a high priority be given to the development of new behavioral assays in these areas.

Funding Mechanism

We recommend that the RO3 or R21 mechanism be used to support these types of pilot projects. We encourage modification of the usual application format such that brief (5-7 page) proposals which are reviewed rapidly and do not require extensive pilot data be considered. We recommend that funding be identified to support approximately 10 applications, at a direct cost of $50 K per application per year for a maximum of two years.

3. **To facilitate training endeavors in complex behaviors**

There is an increasing interest and need for training in the behavioral analysis of mutant mice. The few existing courses are extremely popular and cannot accommodate the interested applicants on a yearly basis. We recommend that funding be identified to develop and implement new course and workshop development for the phenotypic analyses of inbred strains and mutant mice such that the assessment of multiple behavioral domains be available.

Funding Mechanism

It is estimated that a minimum of two additional courses be supported by meeting grants (R13), or other appropriate methods.

BREAKOUT GROUP: Pharmacologic Response
Laurence Tecott, Chair

1. How can reference pharmacokinetic and pharmacodynamic data be efficiently established for different drugs?

2. What are the priority levels (high, medium, or low) and cost/benefit ratios for assays to be included in testing batteries, such that there are no more than 10 high priority assays?

3. Is high-throughput screening practical, and for which phenotypes?

4. Can batteries of assays be constructed such that order effects will not distort performance on subsequent assays?

5. How can the reliability, efficiency, and validity of such batteries be objectively monitored and quantified across multiple labs?

Overview of the Discussion

In this session, strategies were discussed for examining genetic influences on the actions of psychoactive drugs in mice. Initial discussion centered around the identification of pharmacological agents for study. The group then focused on the selection of behavioral assays to be used in the testing of these agents. Considerations in the development of a rational pharmacologic test battery suitable for high throughput screening were discussed. The need to examine influences of genetic background on these pharmacological responses was acknowledged. Finally, the resources required to achieve these goals were discussed.

Identification of Drugs of Abuse

A consensus was reached to focus both on drugs of abuse and on drugs relevant to the treatment of neurobehavioral diseases. The following compounds were considered based on their prevalence of abuse.

*EtOH	*amphetamine	*cocaine
LSD	*PCP	*MDMA (Ecstasy)
nicotine	*morphine	THC

For a pharmacologic test battery, we selected compounds (indicated by *) with varying mechanisms of action that produce robust behavioral effects in assays suitable for high throughput phenotyping. It was recognized that, in addition to their substance abuse liability, some of these agents (e.g., PCP, amphetamine, MDMA) are capable of inducing psychopathology that mimics particular features of neurobehavioral disorders. Thus, genetic influences on these drug responses may be relevant to both substance abuse and other neurobehavioral diseases.

Identification of Psychotherapeutic Drugs

We chose to focus our discussion of psychotherapeutic drugs primarily on those in common use for the treatment of major neurobehavioral diseases. Compounds relevant to the following clinical conditions were considered.

Depression
- *paroxetine: a serotonin-selective reuptake blockers
- nisoxetine: a norepinephrine-selective reuptake blocker
- *desipramine: a tricyclic antidepressant
- phenelzine: a monoamine oxidase inhibitor

Bipolar disorder/mood lability
- lithium
- valproate

Psychotic states
- *haloperidol: a prototypical “typical” antipsychotic agent
- *clozapine: a prototypical “atypical” antipsychotic agent

Anxiety states
- valium: a prototypical benzodiazepine
- *midazolam: a benzodiazepine with greater solubility
- buspirone: a partial 5-HT1A receptor agonist
- *â-carboline: anxiogenic inverse $GABA_A$ receptor agonist
- pentylenetetrazol: anxiogenic $GABA_A$ receptor antagonist

Overeating
- fenfluramine
- amphetamine

Alzheimer’s disease/dementia
- *scopolamine: a muscarinic antagonist known to impair cognition

Seizure disorders
- pentylenetetrazol: $GABA_A$ receptor antagonist

For a pharmacologic test battery, we selected compounds (indicated by *) that produce robust behavioral effects in assays suitable for high throughput phenotyping. In addition to psychotherapeutic drugs, â-carboline and scopolamine were chosen to examine genetic influences on drug effects that simulate psychopathology. Medications used in the treatment of some conditions (e.g., bipolar, panic and obsessive compulsive disorders) were excluded due to the current lack of appropriate animal models.

Toward a Pharmacologic Test Battery

It was recognized that high throughput phenotyping of pharmacologic responses would require cohorts of mice to be treated with multiple drugs. A consensus was also achieved that each animal would be treated with a single dose at the ED50 determined for the appropriate background strain. Order effects were considered to be unavoidable, but information on their magnitude could be obtained. The contribution of order effects could be assessed in inbred strains by comparing the responses of cohorts of animals run through the test battery with those of cohorts run in individual tests. To minimize variability attributable to diurnal influences on drug response, individual assays should be run consistently at the same time of day. A list of pharmacologic responses suitable to high throughput testing is indicated below.

EtOH:	locomotion/exploration*, baseline startle amplitude
amphetamine:	locomotion/exploration, prepulse inhibition of startle (PPI)
cocaine:	locomotion/exploration, PPI
PCP:	locomotion/exploration, PPI
morphine:	locomotion/exploration, and hot plate test
MDMA:	locomotion/exploration
desipramine:	forced swim test
paroxetine:	forced swim test**
haloperidol:	locomotion/exploration, catalepsy, temperature, PPI
clozapine:	locomotion/exploration, temperature, PPI
midazolam:	thigmotaxis in open field
â-carboline:	thigmotaxis in open field
scopolamine:	locomotion/exploration

*behavioral enclosure for monitoring locomotor activity, thigmotaxis, and exploratory nose pokes

**tail suspension test may be preferable if relevant inbred strain data exists

It was recognized that the coordination of a pharmacologic battery with efforts to screen for baseline behavioral abnormalities would allow for the most efficient use of animals. Insufficient time was available to discuss the optimal ordering of the tests or the time intervals between assays. In addition to these tests, it was recommended that drug effects on body temperature be assessed and that samples be taken for assays of blood chemistry and hormone levels.

Drug Testing in Inbred Strains

The interpretation of pharmacological test results in mutagenesis studies requires detailed information regarding the responses of the relevant background strains to the test compounds. A consensus was reached that dose-response data should be collected, with a minimum of 3 drug doses (excluding vehicle). It is also recommended that data be collected for both male and female mice. Because the search for outliers in primary screens requires detailed information regarding the variability and distribution of drug responses, group sizes in the range of 40 mice per strain per dose per sex could be considered. Consensus was also reached that the collection of this data for 10 inbred strains, the “Group A” strains plus AKR, will be sufficient for the vast majority of purposes. Additional recommendations were made that pharmacokinetic data be collected for each drug in each strain and that information be provided regarding the p450 isozyme profile of each strain.

Required Resources

It is recommended that several other compounds in addition to those indicated by * above be studied, but the absence of robust behavioral effects in current assays suitable for high-throughput phenotyping leads to a recommendation that they be assigned a lower priority. These include several drugs of abuse (LSD, nicotine, THC) and psychotherapeutic agents (nisoxetine, phenelzine, lithium, valproate, buspirone, fenfluramine). Development of robust, high-throughput assays for these drugs is recommended, at a cost of $500,000 in direct costs in the first year and for a period of two years. Rough estimates were made of the funding levels required to support high-

throughput efforts. A one-time expense of $200-300,000 would be needed for equipment purchase. The implementation of a behavioral battery consisting of 10 assays, and a testing rate of 10,000 mice per year would require the daily performance of more than 400 assays. At this rate, it is estimated that 15-20 research assistants at $525-700,000 per year would be required for various tasks, including the preparation of drug solutions, the running of behavioral assays, and the analysis and organization of the resulting data. To estimate housing costs, we allow 2 months for acclimation of animals to the behavioral facility and testing in the pharmacologic battery. Yearly housing costs for 10,000 animals, housed 5 mice per cage at $1 per day amount to $120,000.

BREAKOUT GROUP: Imaging and Electrophysiology
Jeffrey Noebels, Chair

1. Why do MRI in the mouse?

2. What are the priority levels (high, medium, or low) and cost/benefit ratios for assays to be included in testing batteries, such that there are no more than 10 high priority assays?

3. Is high-throughput screening practical, and for which phenotypes?

4. Can batteries of assays be constructed such that order effects will not distort performance on subsequent assays?

5. How can the reliability, efficiency, and validity of such batteries be objectively monitored and quantified across multiple labs?

The group discussed the specific issue of applying new imaging technologies as screening assays to accelerate gene discovery in large mouse mutagenesis programs. There was basic agreement that structure-molecular function correlations are critical to phenotyping the nervous system, and that molecular imaging (imaging markers that reflect neuronal activity) could play an important role in both primary and secondary screening. There was little enthusiasm for use of MRI for structural screening, which is done more simply by standard histology techniques. In contrast, functional imaging can be performed either as a survival method using MRI adapted for mice, or as a terminal method by conventional brain sectioning using special stains that mark for neuronal activity (e.g., antibody to the immediate early gene c-fos) or autoradiographic techniques that show uptake of specific metabolic markers (e.g., 2 deoxyglucose).

Survival and non-survival imaging methods offer complimentary approaches to screening. Survival imaging may be better suited for primary screening purposes where detection of an abnormality must be performed in one or a few mice that may required for subsequent breeding. It has the relative advantage of providing a dynamic study for serial studies of development in the same animal, and can be used in intervention studies (imaging before and after a genetic alteration, treatment, drug exposure, etc.). Head stabilizing frames could be developed that allow the larger scale scanning of multiple mice simultaneously. Disadvantages over conventional imaging using brain sections from sacrificed animals include: lower resolution, rarified expertise/availability of the technology, and higher cost. Similarly, non-survival techniques (e.g., 2 deoxyglucose autoradiography on frozen brain sections versus PET studies on living animals) provide the advantages of higher resolution, wider range of functional and structural markers, lower cost, and are widely accessible; however; the primary disadvantage is that the animal must be sacrificed and hence could be less advantageous as a primary screen.

Electrophysiology techniques modeled after those in clinical use are ideally suited for primary screening of mutant mice, and should be used for routine characterization of neurosensory phenotypes.

Recommendations

1). We are still at the early stages of applying functional in vivo imaging technologies to phenotypic screening. At present, the mutagenesis and imaging communities must learn more of each other's needs and capabilities. MRI is available for structure, but is presently inefficient for primary screening. Functional MRI has not yet been adapted for routine use, analysis varies among centers, and algorithms are still under development. Thus, there is a major need to enhance communication between the communities in the form of workshops and symposia to define promising new tools for screening assays. Existing tools may meet the needs of some secondary screens of mouse mutants.

2). Promote novel functional imaging techniques and reagents applicable to screening; e.g., construction of novel reporter strains for assessing gene expression, and synthesis of novel markers for brain functional activity visible with high throughput spectroscopy or MRI.

3). Support further development of high throughput imaging technology and computer algorithms for volumetric differential analysis of data suitable for primary screening; e.g., assembly line microPET, micro-ultrasound, microCT, microMRI.

4). Support continuing adaptation of clinical electrophysiological techniques to mutant mouse screening; e.g., multielectrode EEG, ERG, ECG, VER, ABR, DPOAE, SSER, and EMG.

BREAKOUT GROUP: Bioinformatics and Databases
Nathan Goodman, Chair

1. How can a common vocabulary be established to ensure widespread utilization and efficient searching of a public phenotypic database by as many researchers as possible?

2. How do we assure that this database will be highly accessible and searchable to as many researchers as possible, e.g., should a web-based approach using industry-standard software like Oracle and robust search engines be used?

3. How can quality assurance/quality control be maintained while assuring rapid release of derived and primary data?

4. How can a public database be maintained and sustained long-term?

It is the sense of this breakout group that the difficulty of this database is not qualitatively harder than existing genome-type databases. We also feel that the current requirements and specifications are not well defined and do not address prioritization of information to be included. We discussed using a method common for industry. The standard commercial method for gathering requirements is a defined process involving interviewing target users, review of information to be included and compiling a report that summaries these observations. This report would be great helpful for those putting together a database of phenotypes for the mouse CNS community. However, it was pointed out that this method might be difficult to implement - the BIST proposals may be a possibility. The standard NIH genome method used for database projects is to allow those who are successfully awarded to gather specifications and design the system. The latter method of developing a specification is also acceptable.

The group did not specifically address the four questions because of the lack of clarity and requirements for the proposed database and user community.

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