

# NIDA/NIAAA Training Overview

## Training Goals

The Department of Behavioral Neuroscience is the recipient of pre- and post-doctoral institutional research training grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA). Our focus is on the basic biological processes involved in the etiology of alcoholism and drug addiction. Our general approach is interdisciplinary. The program's goal is to produce specialists in the biological basis of alcoholism and drug-seeking behavior who will be thoroughly competent to teach and conduct research on the problems of substance abuse and addiction at both molar and molecular levels. The program is designed to take full advantage of the unique educational opportunities available in a medical school to train biologically-oriented scientists in a variety of disciplines relevant to neuroscience, including cell and molecular biology, neuroanatomy, neuropharmacology, neurophysiology, genetics, and behavioral neuroscience.

## Training Site

The training program includes investigators with faculty appointments at the Oregon Health and Science University (OHSU), with laboratories there, at the affiliated and physically incorporated Department of Veterans Affairs Medical Center (VAMC), the nearby Oregon National Primate Research Center (ONPRC), and Portland State University (PSU). Several investigators are affiliated with the Vollum Institute for Advanced Biomedical Research (VIABR), a facility established on the OHSU campus in 1987 which concentrates on studies of molecular neuroscience. OHSU has been preparing pre- and postdoctoral students for teaching and research careers in the biological bases of drug-seeking behavior for more than two decades. Scientists based at the VAMC, VIABR, and the ONPRC train students through their affiliations with a basic science department of OHSU, or the Vollum Institute. Participating faculty are in the Departments of Behavioral Neuroscience; Cell, Developmental, and Cancer Biology; Physiology & Pharmacology; Neurology; and the Vollum Institute.

## Level of focus

The strengths and research directions of the training faculty comprise laboratories representing four levels of focus, although most investigators are obviously not strictly bounded by a given level. The first of these is represented by laboratories working principally at the *cellular/molecular/biochemical* level to investigate processes mediating

drug responses. The faculty members most closely identified with this focus include Drs. Buck, Grandy, Jahr, Janowsky, Low, Meshul, Neve, Ryabinin, and Wiren. Studies ongoing in this area concentrate on the effects of acute and chronic drug treatment in a number of systems, including: characterization of key receptor genes such as the dopamine and opioid receptors and the dopamine transporter protein; examining dopamine and glutamate function using chimeras and receptors or transporters modified by site-directed mutagenesis; analyzing transcriptional regulation of endogenous opioid genes; expression of GABA and steroid receptor proteins and RNA derived from genetic animal models of drug sensitivity in *Xenopus* oocytes; studies of the trafficking of fluorescent-labeled proteins in cultured cells, use of microarray analysis to identify genes regulated by chronic drug treatment; biophysical studies of excitatory amino acid receptors using patch-clamp methods; functional studies of expression and enzyme activity for candidate genes identified from gene mapping efforts; studies of null mutant and overexpression transgenic mice; and ultrastructural examination of synaptic alterations in brain using electron microscopy.

The second level of focus is represented by those laboratories studying *systems* mediating drug-related responses at the neurochemical/neurophysiological/neuropharmacological level. Faculty working primarily at this level are Drs. Finn, Johnson, Kelly, Mark, McCleskey, Olsen, Ronnekleiv, and Williams. These studies include: use of in vivo voltammetry and microdialysis to study transmitter overflow; excitatory amino acid receptor, dopamine, and GABA function assessed by quantitative receptor autoradiography, in vitro binding, GTP S binding, immunocytochemistry, and in situ hybridization; opioid regulation of ion conductances (potassium, calcium and other cationic currents) using voltage clamp techniques in a number of cell types; evaluation of non-opioid mechanisms regulating pain circuitry; analysis of dopamine and serotonin circuitry using single cell recordings in brain slices; use of neural ensemble recording to study the influence of drugs of abuse on information processing in the limbic system; the role of neuroactive steroid hormones and stress in drug self-administration and withdrawal studied in vivo and in vitro; the role of potassium channels in hippocampal-dependent learning.

The third area of focus is represented by those investigators studying drug effects at the *behavioral pharmacological/pharmacogenetic* level. This group includes Drs. Belknap, Crabbe, Cunningham, Hitzemann, Phillips, and Raber. These studies are largely at the behavioral and genetic level, including: development of congenic and recombinant congenic strains and mouse lines selected on the basis of genotype at selected markers; relative contributions of initial sensitivity and tolerance to drug dependence, self-administration and withdrawal; chronic intravenous drug self-administration; studies with several other tasks assessing drug reinforcement, including place- and taste-conditioning, oral self-administration, locomotor stimulation, and locomotor sensitization; homeostatic models of drug tolerance and withdrawal, using temperature regulation and ataxia; studies of the role of contextual cues in several learning and conditioning paradigms; epidemiological analyses of drug dependence; and statistical association and linkage analyses to map chromosomal location of genes modulating drug responses using quantitative trait locus analysis. Recently, the gene discovery effort of this group of investigators has been among the pioneering efforts

marrying gene expression array analyses with the more traditional sequence-based QTL mapping methods.

The fourth area of focus includes studies of drug effects at the cognitive neuroscience/human/clinical level. This group includes Drs. Berger, Hauser, Hauser, Mitchell, Oken, and Stevens. Studies by this group involve the use of behavioral tests, EEG, functional magnetic resonance imaging, and PET imaging to evaluate steroid and drug effects in the human brain, to characterize impulsivity in humans and rodents, and to develop novel therapeutics for the treatment of drug abuse.

## Common Research Themes

The studies ongoing in the laboratories of the Training Faculty have several commonalities, reflecting a high degree of collaboration among laboratories. Four areas of commonality are selected from the many currently in place to illustrate the collaborations in Portland. Twelve investigators are actively studying dopaminergic systems, which are considered central to most current theories of the neurobiology of drug abuse. These ongoing studies span the range from molecular biology to behavioral pharmacology and genetic mapping. Furthermore, the specific collaborations in place combine different levels of approach, taking advantage of the range of faculty expertise.

A second strong theme common to the training faculty is the use of genetic tools to study the problems of drug abuse. Fourteen of the faculty are actively employing genetic strategies, with a strong focus on studies whose goals is to map drug-sensitivity genes to particular chromosomal locations using Quantitative Trait Loci (QTL) methods. The homology between human and mouse chromosome maps will allow the eventual mapping of these genes to the human chromosome through syntenic mapping. Several candidate QTLs have been identified with a high degree of statistical certainty, and faculty and trainees are now pursuing the identity of the mapped genes. Thus, activity in the genetics group is beginning to integrate the studies of single genes from the behavioral pharmacogenetic level of mapping to the molecular biological study of gene function.

A third theme common to ongoing research in the laboratories of several members of the training faculty is the study of learned and unlearned determinants of responses to drugs, particularly their rewarding effects and drug self-administration. A number of animal models differing genetically are used in these studies. Finally, a fourth example of commonality is in the area of opioid systems, where seven members of the training faculty have studies underway at all levels of analysis.

These examples are illustrative of the large number of collaborative interactions among training faculty that have already involved our pre- and postdoctoral trainees. In fact, the implementation of this training program has fostered the development of many new collaborations, especially between faculty working at different levels of analysis. The

collaborative interactions involving NIDA trainees are clearly reflected in the list of Trainee Publications.

## Other Trainee Activities

Trainees have access to and participate in a variety of other scientific and academic activities on the OHSU campus. Activities of our research training program overlap and are coordinated with those of the Portland Alcohol Research Center (PARC), and the Methamphetamine Abuse Research Center (MARC). Postdoctoral trainees organize and run a monthly journal club attended by trainees and faculty, where current papers are discussed. At a biweekly neuroscience seminar, faculty and postdocs present their ongoing research in a very informal setting. The basic science departments and the Vollum Institute have frequent seminars by outside speakers in a range of neuroscience disciplines, and the training grants and PARC sponsor many visiting speakers each year. Finally, there is an annual 1-day retreat where trainees and faculty present data and discuss programmatic issues.