

Integrative and Organ Systems Pharmacology: A New Initiative from the National Institute of General Medical Sciences

Normal physiology, pathology, and pharmacology reflect not only interactions between molecules and cells, but interactions of multiple tissues, organs, and organ systems as well, yet for the past several decades, much attention has been focused on studies at the cellular and molecular level. Bioinformatic and genomic approaches are suggesting new molecular targets at an ever increasing rate, and the ability to develop genetically modified organisms has outpaced the ability to characterize the phenotypic changes in these organisms. Hypotheses generated by *in vitro* studies or by computational biology and systems approaches to the integrative behavior of living systems need to be tested in the actual living organism. Interest is also growing in behavioral and neurobiological phenomena that can only be studied in relatively intact systems and living organisms. Thus, there is a growing recognition of the need for functional analysis of biological systems to connect results at molecular and cellular levels to the expression of genetic and environmental determinants in the whole organism (1–2).

Pharmacologists experienced with *in vivo* models form an integral part of every drug discovery and development project and are essential to assuring that only safe and efficacious lead compounds go forward to clinical trials. New tools, such as microdialysis and imaging methods, have become available that enhance the collection efficiency and value of pharmacological data obtained *in vivo*. Discoveries in the areas of chemistry, genomics, and pharmacogenetics have accelerated the rate of research and have increased the demand for integrative and organ systems pharmacologists in the pharmaceutical industry.

Unfortunately, current academic infrastructure may not be able to meet the demand for appropriate training in this area. The success of reductionist approaches based on molecular and cellular methods has resulted in the displacement of many of the researchers formerly engaged in integrative and organ systems studies. Activism, while usefully raising consciousness about the importance of using animal subjects responsibly, has in some cases become an obstacle to the conduct of needed research. The cost of animal subjects research has increased and the use of animal subjects in basic medical and graduate instruction has been significantly curtailed.

The National Institute of General Medical Sciences (NIGMS) has fielded the concerns of academic and industrial scientists about the training received by current students in the area of integrative and organ systems sciences. Most students receive limited training in physiology and integrative pharmacology. Even within the discipline of pharmacology, not all students gain significant

hands-on experience with *in situ* organ system and *in vivo* animal models. Graduates need to have sufficient understanding of how to choose and use models that appropriately reflect the human condition under study. Furthermore, students need the skills to communicate with other scientists across the breadth of science required for translation of research results into health benefits, from isolated molecule to whole animal and human clinical research.

A broad coalition of scientific organizations, led by the American Society for Pharmacology and Experimental Therapeutics (ASPET) and the American Physiological Society (APS), have called for increased support of research and training in the integrative and organ systems sciences (3). NIGMS staff have met with representatives of these societies and other industrial and academic scientists on multiple occasions to discuss the issues (e.g., 4–6). Data and opinions presented at these meetings contributed to development of the new NIGMS initiative in this area.

NIGMS defines Integrative and Organ Systems Pharmacology (IOSP) as “pharmacological research using *in vivo* animal models or substantially intact organ systems that are able to display the integrated responses characteristic of the living organism that result from complex interactions between molecules, cells, and tissues.” Such studies are important because isolated molecules and cells *in vitro* do not necessarily reflect the properties that they possess *in vivo* and cannot adequately reflect the function of intact tissues, organs, and organ systems. At its January meeting, the NIGMS Advisory Council approved a plan to solicit proposals for Education Projects that will provide students with the skills needed for studies of integrative organ system and whole-organism biological responses to drugs and other physiological perturbations. A Request for Applications (RFA) is expected to appear in the NIH Guide this spring¹. NIGMS anticipates making one to three awards of \$100,000–200,000 per year for a period of three years. The awards will support short courses to provide intensive instruction in an immersion environment beginning in the summer of 2005.

The objective of the short integrative and organ system courses will be to restore the balance between *in vitro* and *in vivo* approaches to science. These courses will develop, implement, and disseminate an appropriate, innovative curriculum to teach basic concepts and experimental techniques. They are expected to stimulate IOSP activity at multiple institutions through generation of student interest and encouragement of institutional commitment. NIGMS anticipates that brief but intensive courses offered during the summer will allow students to participate without disrupting their progression through training at their home insti-

¹ Details concerning the mechanism of grant support; allowable costs; available funds; institutional and principal investigator eligibility; special requirements; and application, review, and award procedures are detailed in the RFA

tutions. Follow-up experiences at either the home institution or through industrial internships will be important to allow students to utilize and further develop their skills. Industrial follow-up experiences might be coordinated by the course organizers. Interested students will likely be drawn primarily from graduate programs in pharmacology, physiology, toxicology, and related disciplines. However, the courses should also attract students at all career stages, and from industry and government as well as from academia. The courses should foster students' ability to assume leadership roles in all three sectors by exposing students to biomedical fundamentals not currently stressed at many institutions in the United States, such as:

- Strong connections between in vitro, organ function in situ, and in vivo results;
- translational research and safety and efficacy in drug discovery and development;
- animal model options and the suitability of a given model for a particular purpose;
- experience with small-animal models and exposure to large-animal models;
- responsible conduct of research and the ability to articulate the need for IOSP work; and
- communication of science across a broad spectrum of research activities.

The short courses will need to introduce concepts as well as provide for acquisition of initial hands-on skills with a number of organ system and intact animal model methods. A combination of lectures, labs, demonstrations, and seminars might be used. Allied disciplines such as physiology and other related areas of integrative and organ systems sciences will need to be included as they form the underpinnings of in vivo pharmacology. Given the importance of toxicology to industry, this topic should also be of considerable interest. The short courses should not merely cover the necessary techniques to execute a particular protocol. Rather, they should provide an understanding of the strengths and weaknesses of particular models and the important concepts needed to design meaningful experiments. The courses should provide not only familiarity with systems that are inherently integrative in their function, but should enhance the ability of the scientist to integrate information about systems. Although much attention may be focused on mouse and rat models, inclusion of other species in some capacity would be highly desirable.

Any academic, industrial, or independent research laboratory or institution might serve as the home for a short course. However, the commitment of a significant number of other institutions to the enterprise will be of great benefit. Such participating institutions could provide faculty, equipment, supplies, and most importantly, a commitment to facilitate the participation of their students. Industry remains one of the research settings in which integrative and organ systems sciences still play a major role. There are a number of ways that industry might usefully con-

tribute to a short course. Researchers from industry might serve as faculty members. A short course might make use of industrial laboratory facilities. Industry scientists might serve as part of an organizing committee and industry scientists might be welcomed as students. The possibility of co-sponsorship is obvious; however, even greater impact might be achieved by coordinating with academic institutions to provide follow-up opportunities for industrial research experiences utilizing in vivo and organ systems models.

The success of this program will depend on appropriate leaders coming forward to serve as course directors, which will require a significant commitment of time and effort. If other short courses may be taken as a model, the involvement of investigators from multiple institutions (as faculty and as mentors of participating students) will be essential. Preliminary indications are that students from multiple institutions will be interested in taking this training. The commitment of mentors to projects that will continue the training of students in integrative and organ systems sciences will be vital to sustaining skills learned in the short course. DOI: 10.1124/mi.4.2.1

References

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Peter C. Preusch, PhD
Pharmacological Sciences
Training Grant Program Director
NIGMS/NIH
Department of Health and
Human Services
E-mail preuschp@nigms.nih.gov