ORI NEWSLETTER

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MANAGEMENT OF BIOMEDICAL RESEARCH LABS REQUIRES MULTIPLE SKILLS

Besides possessing the scientific skills needed to obtain the grant that initially establishes the laboratory, the director needs to exercise the skills of research, personnel, and business managers to successfully operate a biomedical research laboratory.

These skills are especially important in the current research environment, which is characterized by more emphasis on research with direct relevance to human disease, and increased dependence on technologies too complex and expensive to be supported in individual laboratories. The environment has also expanded opportunities for effective collaboration, increased institutional management of research faculty, and led to more regulation and oversight of research. Additional pressure to generate faculty salary support from grants, more emphasis on patenting and licensing research results, and less institutional and departmental support for core facilities, professional enrichment, and grant administration has also resulted.

These characteristics of the current research environment emerged from presentations made to 140 attendees on the role of laboratory directors, mentoring, managing the research agenda, quality control, data management, collaborative research, and assignment of credit at the first national Conference on the Management of Biomedical Research Laboratories. The conference was held October 1-3 in Tucson, co-sponsored by the University of Arizona and ORI. Proceedings are in preparation.

"The Director must clearly articulate the laboratory's scientific goals and their relevance to local and national health issues, constantly integrate new technologies into the group's repertoire, redirect the research agenda as new discoveries are made, ensure the timely publication of fundamental results, act upon results and concepts with translational or commercial potential, and connect the group to the world community of biomedical scientists through local, national and international collaborations," Janet Oliver, University of New Mexico, said. "The continuous challenge of the laboratory director is to maintain a stable base of diversified funding for contemporary research."

Fred Grinnell, University of Texas Southwestern Medical Center, said laboratory directors must pick their research topics with care because "choosing to test a hypothesis means making a commitment of time, energy, and money." Three questions should be asked about a proposed hypothesis: Is it unsolved? Is it worth solving? Can I do it?

"It is one thing to have an idea, but quite another to be confident that it is the unique and correct explanation of a phenomenon and to commit oneself to act on that conviction." Grinnell said. "Success depends on commitment, entails risk, and requires the laboratory director to become an

advocate for his/her beliefs."

Mentoring is an important skill for laboratory directors because it enables them to attract needed human resources. "A good mentor seeks to help a student optimize an educational experience, to assist the student's socialization into a disciplinary culture, and to aid the student in finding suitable employment," David Challoner, University of Florida, said. "Mentors can make crucial contributions to a postdoctoral student's career in helping to focus goals and to find the next position." Mentors should help graduate students "to finish their degree program in a timely fashion."

Alan Schechter, NIDDK, conceded that "there are no easy or universal solutions to mentoring problems" and acknowledged that "institutions must tread a delicate balance between their responsibilities to their faculties and to their trainees" in devising solutions. Schechter reported that NIH is preparing guidelines on mentoring and training in its intramural research program "as a result of increased sensitivity to difficulties inherent in training experiences."

Tom Davis, University of Arizona, recommended the good laboratory practices (GLPs) developed by the Food and Drug Administration (21 C.F.R. Part 58) and the Environmental Protection Agency (40 C.F.R. Part 792) as quality control measures. The standard operating procedures are reproducible methodologies and serve as excellent training tools, Davis said. Also, students trained in GLPs find jobs quicker, equipment maintenance and use can be readily monitored, and the preparation of papers and final reports is easier.

Data management is becoming an acute problem for laboratories and institutions because of the growing complexity of research data that must be recorded, organized and managed. The data complexity is fueled by an increasingly complex social organization of research, the growing entrepreneurial nature of biomedical research, and greater litigiousness in the research community, according to David Wright, Michigan State University.

"The consequences of poor recordkeeping and data management are more severe than ever before. Sloppy or merely inadequate recordkeeping renders the investigator much more vulnerable to allegations of fabrication or falsification of data, and institutions liable to lose patent claims, perhaps worth millions of dollars," Wright said. "Pressure is increasing for the rigor of industrial research data policies as more research results are translated into the intellectual property market place."

Wright declared that data should "be recorded with sufficient rigor, clarity, and thoroughness and maintained with sufficient organization and integrity to allow disinterested investigators within the same field but outside the project to understand, to evaluate and, if necessary, to replicate the research."

A data management policy should address the persons and research covered, the definition of

data, recording of data, ownership of data, access to data, retention of data, and the maintenance of data, says Walter Meyer, University of Texas Medical Branch, Galveston.

Laboratory directors are likely to become involved in collaborations more frequently because "modern biomedical research demands a wide variety of technologies and expertise, which is not usually possessed by individual investigators," Bernard Janicki, Dana-Farber Cancer Institute, said.

Janicki, however, warned that a variety of conflicts occur, "Most often, inter-personal differences center on leadership disputes involving the credit and attribution for discoveries. More serious conflicts involve intellectual property rights, including inventorship and ownership of patents, and subsequent disputes over licensing and royalty distributions.

"Conflict prevention and resolution depend on well-defined roles and responsibilities for the participating investigators. Issues of leadership, authorship order and intellectual property management can, and should be, clarified and documented at the beginning of the collaborative arrangement. Oversight by institutional leadership and clearly defined institutional policies and procedures are essential to successful management of collaborative research activities." Janicki said.

"Assignment of credit is one of the most frequent causes for dispute among biomedical scientists," declared Francis Macrina, Virginia Commonwealth University. Credit problems may arise over papers, grant applications, presentations of research at scientific meetings, and in choosing areas of research and methodology.

The problem may be intractable because "it is often difficult to document relative contributions to a project and because the standards for assigning credit are highly variable," Michael Kalichman, UC-San Diego, said. Options for decreasing the frequency and severity of disputes include written guidelines, arbitration mechanisms, discussing credit assignment early and often during the project, and training in conflict resolution. Other approaches include creating new ways to define credit and changing criteria for promotions and funding.

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ORI INTRODUCTORY WORKSHOP PLANNED FOR FEBRUARY IN CALIFORNIA

Allegations of data fabrication, falsification, or plagiarism in scientific research happen rarely at any particular institution. This means that although the institution is primarily responsible for investigating any allegations, most institutional officials have not had any significant previous experience in resolving these issues completely and fairly.

To assist institutions, ORI, University of California, San Diego, the University of California, Los Angeles, and the University of Washington, are co-sponsoring an introductory workshop on

February18, 1999, at the Radisson in La Jolla, CA. The workshop is primarily designed for Institutional Misconduct Officials who are responsible for ensuring institutional compliance with the PHS regulation related to scientific misconduct (42 C.F.R. Part 50, Subpart A), including responding to allegations, but will also be helpful to institutional research integrity officers, inquiry/investigation committee members, administrators, and legal counsel.

Practical advice for handling particular case situations will be highlighted, and participants in the workshop will have an opportunity to share their experiences in resolving misconduct allegations at their particular institutions. The workshop also will provide institutional officials with basic information and practical advice for meeting the regulatory requirements placed on institutions.

The workshop will open with a review of the requirements for maintaining eligibility for PHS funding, including the development of written policies for responding to allegations of scientific misconduct. Next, ORI staff will discuss conducting inquiries and investigations in response to allegations of scientific misconduct, and will highlight particular legal issues that need to be considered when allegations are investigated.

Luncheon discussion groups will afford participants the opportunity to focus on specific issues of interest to them, such as the importance of sequestering evidence to protect all parties, as well as the need for confiden-tiality, thoroughness, and objectivity in promptly investigating allegations. In the afternoon, the importance of protecting the position and reputation of both complainants and respondents will the explored.

ORI staff will also review the general process for Federal oversight and resolution of misconduct cases. Examples will be provided of the various types of PHS and institutional administrative actions that may be implemented if it has determined that misconduct has occurred.

For registration or more detailed information, including the workshop agenda, see ORI's home page (http://ori.dhhs.gov).

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1998 ANNUAL REPORT FORM WILL BE MAILED BY JANUARY 11; DUE BY MARCH 1

ORI will mail the 1998 Annual Report on Possible Research Misconduct forms to institutions no later than January 11, 1999. Institutional officials should request a replacement copy of the form if it has not been received by January 31, 1999.

ORI would like to achieve an 85 percent response rate by March 1, 1999, to eliminate the necessity of mailing a second request. The initial response rate for the 1997 Annual Report was 69%; a second mailing raised the response rate to 86%. Assurances were inactivated for 443 institutions that did not respond to either request for the 1997 Annual Report.

Any misconduct activity reported in the Annual Report must meet two criteria: the alleged misconduct must fall under the PHS definition of scientific misconduct and the questioned research must be funded by the PHS.

The 1998 form is identical to the previous year except for two clarifications. The question concerning bad faith allegations was changed to ask "whether an institution determined if any allegation was made in bad faith." This change was made to clarify that ORI is seeking this information only if the institution has determined an allegation was made in bad faith. ORI is not requiring institutions to make such determinations. Many institutional policies warn that bad faith allegations may be subject to disciplinary action. However, only one institution reported that an allegation was determined to be made in bad faith in 1997.

The second change involved the request for the e-mail address of the responsible official which changed from "Internet" address to the "e-mail" address because some institutions last year reported their web page address. About 2,300 institutions submitted the requested e-mail address on the 1997 form. ORI is building an electronic network to facilitate rapid communication with responsible officials, either individually or en masse, at a lower cost. Institutions that have not submitted the e-mail address of their responsible official are urged to do so.

Although the number of erroneous and incomplete reports has declined considerably, they remain a problem. In 1997, 107 institutions that have an institu-tional policy for responding to scientific allegations on file with ORI indicated that they did not have a policy or did not answer the pertinent question. Forty-five forms were not signed and had to be returned. Sixty-three institutions neither reported any misconduct activity nor checked the box indicating that they did not have any misconduct activity to report.

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FINDINGS REPORTED FROM 5-YEAR STUDY OF CLOSED MISCONDUCT INVESTIGATIONS

Seventy-one percent of the researchers found guilty of scientific misconduct in the 150 investigations closed by ORI from 1993 through 1997 were debarred from receiving Federal funds for periods ranging from 18 months to 8 years. The investigations resulted in 76 findings of scientific misconduct (51%) and 74 findings of no misconduct (49%).

Falsification was the most frequent type of misconduct that resulted in an investigation; it was involved in four of every five investigations either alone or in combination with other types of misconduct, especially fabrication. Fabrication was the second most frequent type of misconduct that resulted in an investigation; plagiarism was third.

ORI received about 1,000 allegations during the 5-year period, which resulted in the opening of 187 cases and the closing of 218. More cases were closed than opened because ORI inherited cases from a previous office. The 218 cases included 68 inquiries and 150 investigations and resulted in 142 findings of no misconduct or no investigation warranted (65%) and 76 findings of misconduct (35%).

These are some of the findings of a study of descriptive statistics that were published in the ORI annual reports from 1993-1997 inclusive. The study report will be posted on the ORI web page, and copies of the report will be available upon request from ORI.

The primary responsibility of institutions to conduct investigations was progressively affirmed by ORI during the period as the percent of extramural investigations conducted exclusively by institutions steadily rose from 64% to 96%. The primary site of the investigations was medical schools (68%) followed by independent hospitals (11%) and research organ-izations, institutes, and laboratories (10%). Institutions imposed nine types of sanctions on respondents found guilty of scientific misconduct. The most frequent sanction was termination of employment.

Respondents were primarily males holding a Ph.D. or M.D. degree. More than three-fourths of the allegations were made against associate professors (27%), professors (19%), postdoctoral fellows (19%), and technicians (13%). Fifty percent of the misconduct findings were made against postdoctoral fellows (28%) and associate professors (22%) while 59% of the no misconduct findings involved associate professors (31%) and professors (28%). Allegations were most frequently supported against students, (73%), postdoctoral fellows (66%), and technicians (62%) and least frequently supported against professors (19%) and assistant professors (29%).

Like respondents, whistleblowers were primarily males holding a Ph.D. or M.D. degree. Senior personnel (deans, professors, associate professors) accounted for 47% of the whistleblowers, junior personnel accounted for 21%. Data on about 30% of the whistleblowers were not available. The support rate for allegations made by whistleblowers in most academic ranks was about 50%. Students, however, had a support rate of 100% and technicians had a support rate of 20%.

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WISCONSIN PROFESSOR FACING $100,000 FINE

Prosecutors will recommend that the maximum $100,000 fine be imposed on Leon Shohet, an engineering professor at the University of Wisconsin at Madison, who pleaded guilty to a misdemeanor charge of using false information to obtain research grants from the National Science Foundation (NSF), according to *The Chronicle of Higher Education*.

Professor Shohet reportedly inflated the number of corporate partners in the Engineering

Research Center for Plasma-Aided Manufacturing to increase the chances of receiving grant money. A university official said the respondent did not intend to deceive NSF.

The U.S. Attorney for the Western District of Wisconsin said the case "sends an unambiguous message to academia and beyond [that] regardless of one's position, lying to obtain money for any purpose will not be tolerated."

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UNIV. OF MINNESOTA PAYS $32 MILLION IN *QUI TAM* SUIT; DROPS SECOND LAWSUIT

The U.S. Government and the University of Minnesota (UM) have settled two lawsuits, *U.S. ex rel. Zissler* v. *University of Minnesota* and *University of Minnesota* v. *Shalala*, stemming from government allegations that accused UM of fraud and misuse of Federal grants and profiting from the sale of experimental drugs. (See *ORI Newsletter*, December 1997.) On November 17, the parties filed a joint notice of settlement and stipulation of dismissal.

In *Zissler*, the United States alleged that UM violated the False Claims Act, the Food, Drug and Cosmetic Act, the Public Health Service Act, and Medicare statutes, and was liable under these statutes and common-law theories of unjust enrichment, mistake of payment, and breach of fiduciary duty for: 1) illegally earning profits from sales of antilymphocyte globulin (ALG), an experimental transplant drug; 2) failing to report $86 million in program income illegally earned from these sales; 3) misuse of $2.3 million in grant funds; 4) misuse of $628,000 in funds under 28 other Federal grants; 5) failing to obtain informed consent from ALG recipients or report adverse reactions to the Food and Drug Administration (FDA); 6) obtaining Medicare reimbursement; and 7) permitting kickbacks.

UM agreed to pay $32 million in settlement to the United States, the largest amount ever recovered in a case involving NIH grant funds. The relator, James Zissler, will receive $1.5 million of that amount. UM also agreed not to continue its fight in *Zissler* to overturn a decision by the U.S. Court of Appeals for the Eighth Circuit, which held that States are subject to the False Claims Act. As part of the settlement, UM also agreed to dismiss its appeal pending before the Eighth Circuit in *Regents of the University* v. *Shalala*. In that companion case, UM appealed the dismissal of its challenge of administrative actions taken against it by NIH in the wake of Zissler to improve the University's grant administration practices.

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CASE SUMMARIES

Katrina Berezniak, M.A., University of Missouri-St. Louis (UMSL): Based on a report from UMSL, Ms. Berezniak's own admission, and information obtained by ORI during its oversight review, ORI found that Ms. Berezniak, a former Research Assistant, Department of Psychology,

UMSL, engaged in scientific misconduct in clinical research supported by a National Institute of Mental Health (NIMH) grant.

Specifically, ORI found that Ms. Berezniak falsified the scoring of taped interviews of nine subjects. The scoring was conducted to measure inter-rater reliability in determining whether the subjects had post-traumatic stress disorder. The falsified data did not appear in any publications nor were they included in the study's database.

Ms. Berezniak accepted the ORI finding and entered into a Voluntary Exclusion Agreement with ORI in which she voluntarily agreed, for the 2-year period beginning September 9, 1998, to exclude herself from serving in any advisory capacity to the PHS; and any institution that submits an application for PHS support for a research project on which her participation is proposed or uses her in any capacity on PHS-supported research, must concurrently submit a plan to the funding agency, with a copy to ORI for supervision of her duties.

Ms. Eileen Glennon, Harvard Medical School (HMS) and Brigham and Women's Hospital (BWH): Based on a report from HMS, and information obtained by ORI during its oversight review, ORI found that Ms. Glennon, former research technician, Endocrine-Hypertension Division, BWH, engaged in scientific misconduct in certain biomedical research supported by grants from the National Heart, Lung, and Blood Institute and the National Center for Research Resources.

Specifically, Ms. Glennon fabricated data to plot standard curves while conducting radioimmunoassays to determine angiotensin II concentrations. When the assays appeared not to be working in approximately half of the assays over a 1-year period, she used numbers from previous standard curves and then used the fabricated standard curve to determine the concen-tration of angiotensin II, thus producing false experimental results. Ms. Glennon cooperated fully with the institutional inquiry panel and admitted her acts.

Ms. Glennon accepted the ORI finding and entered into a Voluntary Exclusion Agreement with ORI in which she voluntarily agreed, for the 3-year period beginning November 13, 1998, to exclude herself from serving in any advisory capacity to the PHS; and any institution that submits an application for PHS support for a research project on which her participation is proposed or which uses her in any capacity on PHS-supported research, or that submits a report of PHS-funded research in which she is involved, must concurrently submit a plan for supervision of her duties to the funding agency for approval. The supervisory plan must be designed to ensure the scientific integrity of Ms. Glennon's research contribution. The institution also must submit a copy of the supervisory plan to ORI.

George A.S. Park, M.S., Wadsworth Center, New York State Department of Health (WC/NYSDH): Based on Mr. Park's own admission, information obtained by ORI during its oversight review, and a report prepared by WC/NYSD and accepted by the University at Albany,

State University of New York (the awardee institution), ORI found that Mr. Park, a former research technician, WC/NHSDH, engaged in scientific misconduct in research supported by a grant from the National Institute of Environmental Health Sciences (NIEHS). ORI acknowledges Mr. Park's cooperation with the Wadsworth Center.

Specifically, Mr. Park falsified high pressure liquid chromatography data. The data were collected over an 8-month period in connection with a project to demonstrate the estrogen-like neurochemical and reproductive effects of the major metabolite of 3,4,3',4'-Tetrachlorobiphenyl. The falsified data were presented at the Dioxin '97 conference in Indianapolis, Indiana, in August 1997 and published with the conference proceedings in *Organohalogen Compounds* 34:125-128 (1997). The conference organizer was notified of the falsifications in the presented data and published abstract.

Mr. Park accepted the ORI finding and entered into a Voluntary Exclusion Agreement with ORI in which he voluntarily agreed, for the 3-year period beginning August 31, 1998, to exclude himself from serving in any advisory capacity to the PHS; and any institution that submits an application for PHS support for a research project on which his participation is proposed or which uses him in any capacity on PHS-supported research, must concurrently submit a plan to the funding agency for supervision of his duties, with a copy to ORI.

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TIPS FOR SEQUESTRATION OF PHYSICAL EVIDENCE IN SCIENTIFIC MISCONDUCT CASES

This is the first of several articles on the importance of evidence management in misconduct cases. It is intended to provide some suggestions on the seques-tration of data that will be useful to institutions conducting misconduct inquiries and investigations. Experience has shown that prompt and complete sequestration of physical evidence is vital for resolving misconduct allegations. If evidence is not sequestered systematically or promptly, with an identifiable chain of custody, the integrity of the evidence can be questioned, creating avoidable complications in misconduct cases. Attention to detail is vital and it is better to secure more, rather than less, evidence and corroborating information. Proper evidence management protects the research and those involved.

First, know and understand the authorities which permit sequestration of evidence. According to PHS grant policy, data and any products generated under a grant or cooperative agreement belong to the grantee institution, not the principal investigator.

Prepare the formal notification to the respondent about the inquiry. Notification should identify the applicable authorities, the nature of the allegations, the process to be followed, and the rights of the respondent.

Data sequestration should take place concurrent with notification. As soon as the allegation has been assessed, determine the supervisory authority over the individuals from whom evidence is to be secured. Consult with legal counsel for the institution about the proper institutional procedures to follow. Confidentially arrange with the supervisor for contact with the respondent and for access to the data and related evidence. Decide the best circumstances to meet the needs to protect the integrity of the evidence and provide for discreet, confidential, timely, and efficient sequestration. It is also generally helpful to have the supervisor accompany the official who is authorized to sequester the data and evidence.

Assemble staff who will assist you. Prepare lists of items to be secured. If appropriate, identify an "expert" who understands the nature of the research and the laboratory setting, and ask this expert to identify the possible types and sources of evidence to be secured. Collateral evidence, such as centrifuge logs, order forms, telephone notes, and examples of comparison information should be gathered at the same time. Decide who will accompany and receive material from each staff member and where the evidence will be stored. Ask the respondent to cooperate with officials and identify all potential evidence at this time. Emphasize that evidence offered later in the process may be given less weight.

Keep track of all records and evidence. Use custody forms, labels, markers, folders, envelopes and other containers, computer equipment, disks, tapes, etc. For notebooks, folders, etc., count the number of pages and make sure each page has a unique identifier. It is generally wise to inventory sequestered documents. The authorizing official should sign each receipt and request that the respondent countersign. The official should also provide copies of the receipt forms to the respondent. The respondent should be assured access to the research records under supervision or copies of records necessary to continue research projects during the period the original evidence is sequestered.

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CONFERENCE PROPOSALS DUE FEB. 1

ORI is seeking proposals from institutions, professional associations, and scientific societies to collaborate with ORI in developing a confer-ence or workshop on scientific misconduct allegations or promotion of research integrity. Generally, available funding would be from $5,000 to $20,000.

February 1, 1999, is the due date for conferences proposed for Sept. 1999 - Aug. 2000. Proposal instructions are available on ORI's home page (http://ori.dhhs.gov) or by calling Dr. Alicia Dustira at (301) 443-5300, e-mail: adustira@osophs.dhhs.gov.

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