# Browsing the NIH Classifieds:

## "National research institute seeking a model organism…"

By Peter Colabuono '04

Research in the biological sciences favors several organisms for study. The specific benefit derived from using a particular model organism depends on the focus of the study, but special characteristics usually include transparency (literally), ease of system manipulation, possession of an extensively sequenced genome, or mapped cell lineages. Eventual medical applications drive the bulk of this research, so organisms with biology similar to that of humans are preferred. Model animals, as they are also referred to, can then be used to elucidate biological pathways in humans. In vivo studies are important because conclusions of research carried out on cells in isolation cannot always predict the interactions of complex networks.

Dartmouth models include swine, mice, zebrafish, yeast, drosophila, neurospora, C. elegans, and arabidopsis. However, the definition of model is a loose one. How does an animal reach model status? Furthermore, how does one begin to conduct research on an organism that is not considered a model? In order to answer these questions, we turn to the process of finding, applying for, and obtaining grants. We find that grants and the institutions that provide them not only fuel research, but play a role in determining which paths research follows.

For a researcher at Dartmouth, the first step in applying for a grant is communicating with the Office of Grants and Contracts. In the past years, faculty duties have changed in that they must now be aware of the frequent changes in requirements and standards in applying for grants. As it is, an "NIH guidelines" report, published weekly, addresses the recent addenda and modifications in NIH procedure. The OGC assists researchers in keeping up to date and inside those guidelines, for example, assuring that data is shared. It also assists faculty in staying knowledgeable of hidden costs they might not recognize: a researcher may have budgeted money aside for disposal of hazardous material, but they might not have taken into account factors like transportation or storage of those materials. Violating EPA guidelines results in hefty fines, so researchers need to account for all preparations before beginning research. The OGC also provides procedural services for the protection of human subjects and for tasks as particular as the use of specific fonts in filling out federal forms. In effect, the OGC provides the stamp of approval on a research proposal, signifying that the College supports the investigator and that it is ready to provide research facilities.

Another important responsibility of the OGC, embodied in the Technology Transfer Office, is its role in assisting faculty in the commercialization of their research. This is becoming an increasingly more important feature of academic research as investigators transform from faculty into entrepreneurs: it has added a capitalistic dimension to academia that has not come without tension. Since publishing and research are now gateways not only to prestige and tenure but to fortune, there is an increased competition for funds. Opponents of such mar-

ket-driven research say that research progresses through sharing and that this market approach will come with a loss of collegiate behavior. Where this has appeared most so far is in conflicts over intellectual property, a recent by-product of the new directions of research. An example occurs in the creation and ownership of reagents: if one researcher loans a reagent to another, and the borrower develops something profitable, to whom should these profits go? Currently, credit goes to the owner. Another problematic area is data sharing. Sometimes, researchers are not required to share their data before publishing. In other instances, such as in work done on the human genome project, data is released according to the "Bermuda Rules"—unfinished data must be released into the public domain within 24 hours of generation, and finished data must be released as soon as completed. Further terms state that no sequence data can be made available to a requester prior to public release, and any publication using sequence data from the database must cite the appropriate sequencing center. Finally, if a clone sequenced through public effort is not available commercially, a requester must make arrangements for the clone to be distributed upon request to the scientific community "in an expeditious manner" immediately upon publication of a research paper using any data generated through the public effort. However, in a recent case at a research center in Woods Hole, Mass., information in a public database was essentially stolen, as the primary researcher claims, and used for publication before the he was able to publish the findings. The rules of publication dictate that once information has been published, nothing of identical content can be published and given credit. Even reading a paper in a public lecture prior to publication annuls the right to publish or patent the finding in other countries.

Another source of tension over ownership arises between companies and researchers whom the companies have funded. To companies, publication is seen as something that compromises their proprietary rights. The OGC acts as a mediator in these situations: at Dartmouth, companies are allowed to review publications and may ask for details to be disguised or removed, but Dartmouth does not give them the right to deny publication. Another course of action for the company is to delay publication for time to establish a patent. In effect, there is creation of fractional ownership: the company is a licensee of the information, but the intellectual property always belongs to the College. At Dartmouth, researchers are given a generous 50/50 split of the earnings, regardless of the total. At other institutions, a sliding scale is used: as revenues go up, the researcher's share goes down. Interestingly, although the host institution owns the information even if research is funded federally, the NIH retains worldwide ownership in that the government retains the right to use the information royalty-free should that ever be necessary.

However, despite these tensions, participation with companies is encouraged. Statistics show that government funded research does not usually reach the market, so partnering with companies enhances the ability for research to reach the market, either through the development of clinical trials or the creation of model drugs. Thus, the role of model organisms in elucidating pathways is an important feature of medical treatment and pharmaceutical therapy. Their use is critical for applying broad findings to realistic, applicable treatment for human beings.

This treatment of human beings is the end goal at the core of all NIH projects. Although the NIH is only one of many sources for research funding, a simple search of "model organism" in the NIH Guide engine returns many "program

announcements" (PAs) that reveal the underlying incentives for the government to fund research. While 75% of NIH funding is open to the typically unsolicited RO1, or investigator initiated proposal, the rest is set aside for projects that the NIH decides upon. The National Institute of Health is made up of 13-19 individual institutions, such as the "National Heart, Lung, and Blood Institute" or the "National Institute of General Medical Sciences." While there are umbrella rules of the NIH that affect all members, each institute currently has the ability to change them. An overarching umbrella rule may be created which would supercede all institute changes—it would most likely deal with topics such as data sharing and ownership.

In the NIH search engine, opportunities rae presented in a way similar to classified ads. "Opportunity for obtaining the sequence of DNA from model organisms that are of particularly high biomedical interest," states one offered by the National Human Genome Research Institute. Another, presented by the National Institutes of Allergy and Infectious Diseases, seeks investigators to employ "appropriate" animal model systems of human viral infections to evaluate the efficacy of antiviral therapies. Yet another presents a "Program Announcement: The zebrafish as an animal model for development and disease research"—this one is particularly interesting as it is offered by a consortium of 17 institutes who support the zebrafish as an animal model for "development, organ formation, behavior, aging, and disease research." Furthermore, this PA is associated with "Healthy People 2010," a Public Health Service-led national activity for setting priority areas. This relation directly relates the use of model organisms with public health initiatives: a considerable amount of funding is directed towards programs that represent each institute's particular interests. In other words, a considerable amount of the current funding offered is interest-driven.

Central to the grant process are the peer-review committees at the NIH that rank incoming requests. Listed in each opportunity or PA are the criteria by which incoming proposals are reviewed: these criteria are universally used by the review committees for assessing NIH grant applications. These criteria typically include: significance, approach, innovation, investigator and environment. In every introduction to this section describing review criteria, the NIH states, "The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health." Although proposals are prioritized based on scores for each criteria, thus allowing proposals strong in certain areas to be considered as seriously as proposals strong in others (eg, high significance, low innovation vs. high approach, low significance), required in all proposals is a strong applicability to medical fields and enhancement in health of the human population. This should not come as a surprise, since the sponsoring parties are national institutes of medicine and desire results they can put to use.

Yet, what are the implications of this interest-driven approach to research on model organisms? On the one hand, there is a definite need to consolidate findings on already established models: several NIH opportunities offer funding for expansion of sequencing programs to include a variety of model organisms. For example, the NIH Mouse BAC Sequencing Program has been expanded to include the sequencing of BAC clones from all species of animals, fungi, and eukaryotic protists (though excluded are plants and prokaryotes). Another opportunity offered by the National Human Genome Research Institute and National Institute of General Medical Sciences proposes to improve model organism databases by sup-

porting the development of robust software components, called modules. These will eventually serve to create generic model organism databases used to integrate genomic and genetic information for additional organisms. Still other projects wish to develop, using model organisms, novel approaches to research. In one instance, an opportunity presented by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of General Medical Sciences seeks to create new methods of studying membrane transport.

However, has a technical definition for model organism been set forth? One opportunity states, "Much of our understanding of biological processes has resulted from the study of model organisms. Research with model organisms has generated large amounts of data." It continues, "Some species are classic model organisms for studying many basic biological processes, while others are studied because of their role in particular diseases or processes." The question arises: if our definition of a model organism is based on past studies, if the awarding of proposals is based on criteria of medical applicability, if proposals are reviewed by peers, and if no acknowledged definition of model organism exists, what means are there for establishing new model organisms or for directing funding towards alternative animal systems?

This subject is not without some controversy. The flow of money into research is considerably interest-driven by both institutes of health and the market. However, who are the institutes or the market to make a claim on what organisms deserve a fair share of sponsorship? Is the scientific community to base current and future study only on the success of organisms in past research? Will limiting research to a small canon of models occur as a detriment to scientific progress? The classification "model" has been used thus far in the comparison between mammalian or vertebrate and human systems. Does this relative definition of model pervade all too frequently?

Within the pursuit of objective science there exists a firm grounding in subjectivity, as the very fuel for scientific inquiry originates out of marketable and medically applicable interests.

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**FURTHER INFORMATION**

Article on Data Sharing in "Science"
Marshall E. "Data sharing. DNA sequencer protests being scooped with his own data." PMID: 11847311. 2002 Feb 15; 295(5558):1206-7.

NIH Guide:
*http://grants.nih.gov/grants/guide/index.html*

NIH Draft Statement on Sharing Research Data:
*http://grants.nih.gov/grants/policy/data_sharing/index.htm*