Commentary

MOLECULAR METABOLISM

New horizons for future research – Critical issues to consider for maximizing research excellence and impact

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1. PROLOGUE

We live in an era in which the pace of research and the obligation to integrate new discoveries into a field's conceptual framework are rapidly increasing. At the same time, uncertainties about resources, funding, positions and promotions, the politics of science, publishing (the drive to publish in so-called high-impact journals) and many other concerns are mounting. To consider many of these phenomena in depth, a meeting was recently convened to discuss issues critical to conducting research with an emphasis on the neurobiology of metabolism and related areas. Attendees included a mix of senior and junior investigators from the United States, Latin America, and Western Europe, representing several relevant disciplines.

Participants were initially assigned to small groups to consider specific questions in depth, and the results of those deliberations were then presented and discussed over several plenary sessions. Although there was spirited discussion with sometimes differing

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opinions on some issues, in general there was good consensus among individuals and the various groups. While the discussions were wide-ranging, we have condensed the topics into three (albeit often overlapping) major areas:

1) General research issues applicable to multiple areas of translational research; for instance, animal models, sex and gender differences, examples of emerging technologies, as well as the issue of data reproducibility and related topics.
2) Funding issues, such as how to secure industry funding without compromising research direction or academic integrity, and the training of students and fellows, with a focus on how to optimally prepare trainees for the diverse potential career paths available.
3) Finally, specific research topics of interest were discussed, including whether peptides or other signaling compounds, or specific brain areas, have "thematic functions" or the challenges associated with investigating the function of G-protein-coupled receptors (GPCR) in the brain.

We consider each in turn.

2. GENERAL RESEARCH ISSUES

2.1. The selection of animal models

One of the first questions considered was how good or bad are our current experimental models? As might be expected, discussion initially focused on rats vs. mice. Mice have many obvious advantages including size, cost per animal, a large genomic database, readily available genetically modified strains, and the ability to use smaller amounts of expensive, hard-to-get experimental compounds. On the other hand, rats perhaps have more translational value because they are often better models for human systems and behavior. For instance, most commonly used laboratory rats (Sprague Dawley, Wistar, Long–Evans) are outbred strains and hence have considerable genetic variation, a feature which for many research questions better represents the genetic heterogeneity and diversity of humans. In addition, in certain situations such as after gastric bypass surgery, rats may better model humans because, similar to humans, the substantial reduction in body weight after gastric bypass surgery is mainly due to a reduction in food intake. In mice, on the other hand, food intake is often scarcely changed after gastric bypass surgery, and the reduction in body weight is largely due to an increase in energy expenditure (for review see [5]). Rats have also contributed to a large and rich experimental database and historic development of scientific theories, especially in behavior, physiology, and brain structure.

Given technological advances in molecular genetics, it may be that the 'genetic manipulation' advantage offered by mice will soon be available - at least to some extent - for rats and other, larger, mammalian species that better model certain features of human physiology and behavior. This is a key factor as many systems remain difficult to assess at the desired level in rodents. Nevertheless, public concerns about the use of invasive experimental methods and, in particular, about performing genetic manipulations in animals larger than laboratory rodents that are phylogenetically closer to humans than mice and rats may hamper the use of such animal models in science. This also relates to the question of whether we should always use the best animal model for a given pathology or whether we should compromise with a species that is more accepted for ethical reasons and perhaps even less expensive?

An important concern for much current research is "translationability" i.e., whether what is found in one species (e.g., rat) is also true of another (e.g., mouse, human). How does this impact or create unnecessary redundancy on the one hand and reduce the likelihood of obtaining funding on the other? For example, if one group reports a phenotype in the mouse, and a researcher using a rat model has the means to extend the findings in a novel way, must s/he first demonstrate the basic phenotype in the rat? Many felt that reviewers demand this intermediate step; i.e., it is widely recognized that there is a concern for cross-species validation that must be considered. And while the goal of such research could be justified as comparative physiology, the actual goal is often more closely aligned with issues of modeling and which species more closely resembles human physiology.

In any case, interfacing well with reviewers (of grant proposals or manuscripts) requires strong justification for any model system. It was the group's consensus that the primary scientific concern should be the significance of the research question being asked. There are no good or bad models per se, but there are better or worse models for a particular question, meaning that the value of the model depends on the nature of the question. There should be well-defined criteria to justify the choice of any model. In this climate of shrinking extramural funding, the choice of one model or another must be clearly laid out for reviewers of research proposals as well as for manuscripts, and journal editors should pay particular attention to these issues.

For translational research, a possible strategy would be that journals and funding agencies could include a section detailing the use and choice of the model and how it relates to human physiology if appropriate. Due to space constraints, such sections could be included in the online supplementary material to allow the authors to offer a detailed explanation of the proposed or used model system, including its strengths and weaknesses. Such an approach would, over time, hopefully generate a consensus or at least partial agreement on the applicability of certain model systems to specific research questions.

There was considerable discussion about the utility of other experimental models, including dogs, pigs, non-human primates, non-vertebrates, and computer models. Many of the trade-offs when using these models are obvious. For example, while non-human primates can model humans more closely than rodents, costs, ethical, cultural, and political issues can make such research prohibitive. Differences among rodent strains are just as likely to be as important as those between any species (e.g. [3]). For some less common models that can be justified for particular questions (for example pigs or other large animals), a strong case can be made for collaborating with researchers in animal science, who generally have access to better facilities in which to conduct such research. On the other hand, for more primitive animal models, such as zebrafish, *C. elegans* and other smaller animals, teaming up with specialists in biology may be a viable option. An excellent, recent review summarizes the strengths and weaknesses of currently used animal models [4]. In general, computer models were deemed to still be somewhat limited for addressing research questions in whole-animal physiology and behavior. On the other hand, they may be useful for specific purposes depending upon what is being modeled. Examples include computational modeling of molecular docking and molecular dynamics in drug design to explore the structure and function of diverse therapeutic targets, or, at the other end of the spectrum, simulation models of obesity trends with a focus on the effects of possible policy interventions on public health and economic outcomes.

The point was made that the use of experimentally modified genes in rodent models is now so common that scientific review groups (e.g., at NIH) routinely assign much lower priorities to proposals that simply describe new phenotypes of genetically modified species. Rather,

