



Standards for Microarray Data

ONE OF THE UNDERLYING PRINCIPLES OF scientific publication in peer-reviewed journals has been the requirement that the authors make available the data and materials necessary for a reader to reproduce the experiment or analysis and to determine whether the data support the authors' conclusions. In many instances, such as DNA sequence or protein structure data, this has evolved into the requirement that the data underlying each published report be deposited in an appropriate international database. For microarray experiments, simply defining the appropriate data has been a challenge, because the large quantity of data generated in each experiment and the typical complexity of the ancillary information needed to interpret the results are unlike anything that has yet faced the biological research community. Databases to hold microarray data and the tools to annotate them properly are under development. As an interim solution, we have described the types of data that are necessary to reproduce and interpret a microarray experiment. It should go without stating that this information is only of value as long as it is available, so every effort should be made to provide stable access to published data until such time as it is available from a public database.

The members of the Microarray Gene Expression Data (MGED) (www.mged.org) society have been working over the past few years to solicit community input in developing standards for the publication of DNA microarray data. The authors of this guide and the MGED society as a whole represent a large cross section of the scientific community that has worked with microarrays. We are convinced of the importance of the issues described and strongly urge journals to use these recommendations when deciding whether to publish a paper using microarray data. In De-

ember 2001, we published a commentary in which we described MIAME—the Minimal Information About a Microarray Experiment (*J*). MIAME is presented as a proposed standard for representation of array data that would be sufficient to allow readers of published reports to replicate the analysis presented and to facilitate the development of novel methods of data analysis by providing access to necessary primary data.

Community response to MIAME was favorable, and many instrument manufacturers, software developers, and international databases moved to adapt their systems to capture and manage MIAME-compliant data. However, by far the most common request from the community has been for a brief set of guidelines that could be used by authors, editors, and referees to try to meet the MIAME data standards.

These requirements can easily be met by adequately describing the experiment, the materials and methods used, and either (i) a relatively simple supplementary Web site or (ii) submission of this information to one of the public repositories [Array-Express (www.ebi.ac.uk/arrayexpress) or GEO (www.ncbi.nlm.nih.gov/geo/)]. Reviewers and editors should strive to help authors meet these requirements and should ensure that, if a publication cannot meet them, there are sound reasons. This document in no way attempts to eliminate the need for editors or reviewers to use their judgment on both the appropriateness of the presentation and the validity of the report, but rather provides a guideline for them in their evaluation of whether or not a manuscript provides as much information as necessary for others to replicate and interpret the analysis presented.

The proposed guidelines, including a checklist for ease of use, are available at www.mged.org/Workgroups/MIAME/miame_checklist.html.

ON BEHALF OF THE MGED:

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Editor's Note: Science supports the evolving standardization of microarray data, one view of which is presented in this letter. We urge our authors to follow the criteria set forth here, although it is not a requirement for publication, and to let us know your experiences and reactions. Please send comments through the debates feature of Science Online (www.sciencemag.org), as they will help us in continuing to participate in this process and establish Science policy.

Energy Expenditure and Treating Obesity

SIGNIFICANT EFFORTS ARE NOW BEING MADE to characterize the molecular pathogenic mechanisms of obesity, possibly leading to effective treatment. Intuitively, obesity can be prevented and treated by either reducing food intake or increasing energy expenditure (*J*). The recent report by P. Cohen *et al.* ("Role for stearoyl-CoA desaturase-1 in

leptin-mediated weight loss," Reports, 12 July, p. 240) indicates a possible therapeutic target to increase energy expenditure, but we feel that some issues need to be resolved before clinical explorations are undertaken.

Cohen *et al.* demonstrate that the down-regulation of stearoyl-CoA desaturase-1 (SCD-1) in hepatic cells leads to an increase in energy expenditure, contributing to leptin-mediated weight loss. They therefore reason that this gene may represent a suitable target for the treatment of obesity, and its modulation seems an effective approach. Although tempting, this speculation may not yield clinical benefits. An explanation for the metabolic effects of SCD-1 down-regulation is a reduction of intracellular levels of malonyl-CoA. If SCD-1 is therapeutically targeted, we reason that the depletion of intracellular malonyl-CoA should also occur in hypothalamic neurons, which are sensitive to leptin (2). In the hypothalamus, however, the reduction of intracellular malonyl-CoA is a strong signal that elicits food intake (3). Therefore, the weight-loss effects of increasing energy expenditure in the liver could be counteracted or blunted by a robust, hypothalamic-driven increase of food intake.

Another relevant issue is the cost-effectiveness of treating human obesity by in-

creasing energy expenditure. Cohen *et al.* find that the down-regulation of SCD-1 increases oxygen consumption by about 50%. In mitochondria, reactive oxygen species (ROS) are generated as undesirable side products of the oxidative energy metabolism (4). Increased energy expenditure results in increased generation of ROS and increased oxidative stress, which in turn are associated with the development of cancer, diabetes, atherosclerosis, and neurodegenerative diseases (4). Thus, it is possible that a long-term increase of energy expenditure may expose obese patients to a risk of developing those same diseases they are trying to prevent by losing weight. An example is given by dinitrophenol. It was introduced into clinical medicine in the early 1930s for weight reduction because it uncouples oxidative phosphorylation, turning excess energy into heat (5). However, it had to be removed from the market because of its severe toxic effects, including fatal hyperthermia in animals (5).

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Response

OUR REPORT AND A SECOND PAPER (1)

establish that the absence of SCD-1 reduces adiposity in two forms of rodent obesity and in lean animals. Although this effect is attributable to an increased rate of energy expenditure, the underlying cellular mechanism(s) and the full complement of tissues that contribute to this increased energy expenditure are as yet unknown. Thus, the extent to which these effects are the result of altered metabolism and/or signaling in the brain, or elsewhere, awaits further experimentation. However, Laviano *et al.* should note that C75, an inhibitor of fatty acid synthase [first described by Loftus *et al.* (2)], has recently been shown to increase peripheral energy expenditure by disinhibiting CPT1 (2, 3). This result is thus consistent with the possibility that SCD-1 deficiency may increase energy expenditure by reducing the intracellular levels of malonyl CoA in peripheral tissues. Alternative mechanisms are also possible. It should also be noted that SCD-1-deficient animals are leaner than controls, despite the fact that these animals are hyperphagic (perhaps, as Laviano *et al.* speculate, secondary to reduced levels of malonyl CoA in the hypothalamus).

The potential use of an SCD-1 inhibitor as a human therapeutic awaits a more complete understanding of the mechanism underlying the effects of SCD-1 deficiency and, more importantly, a clear indication that the inhibition of this enzyme is both safe and efficacious. It is certainly possible that the increased energy expenditure associated with SCD-1 deficiency could lead to unwanted clinical sequelae related to increased levels of reactive oxygen species [a theoretical possibility noted in The Rockefeller University's news release about our report (4)] or any number of other possible unforeseen effects. Whether such effects prove to be similar to those associated with uncouplers of oxidative phosphorylation such as dinotrophenol awaits the results of careful preclinical studies and, if such agents prove safe in animals, safety trials in humans.

Whether the entire obese population, or a substantial subset of obese subjects, should be managed using pharmacologic agents versus lifestyle changes is a major public health issue. Our view is that in an environment where major surgery is often used to treat human obesity, there is a role for safe

and effective drug treatment. Such treatments would be indicated in cases where weight loss is known to improve health. In our estimation, it is premature to predict whether drugs that alter neural signaling or those that act by a different mechanism altogether will prove safe and effective.

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Chemical Emissions: An Ongoing Issue

IN THE SPECIAL ISSUE ON GREEN CHEMISTRY (2

Aug.), the Viewpoint authors emphasize the importance of minimizing risk by reducing hazards from industrial chemicals ("Practical approaches to green solvents," J. M. DeSimone, p. 799; "Biodegradable polymers for the environment," R. A. Gross and B. Kalra, p. 803; "Green chemistry: Science and politics of change," M. Poliakoff *et al.*, p. 807). They illustrate this point with some data from the 2000 Toxics Release Inventory, compiled by the U.S. Environmental Protection Agency (TRI, available at www.epa.gov/tri). A closer examination of the TRI reveals the extent of the emissions problem.

The year 2000 reports document the release of 7.1 billion pounds (3.2 billion kg) of toxicants, of which 26.8% was released into the air. Those "original" industries that have reported their emissions since the first TRI was published in 1987 were the worst offenders. In this group, releases into the air accounted for 48.8%, or 11.1 billion pounds (5.01 billion kg), of on-site and off-site releases. These figures are dwarfed by the total of 37.89 billion pounds (17.19 billion kg) of toxic waste that was reported as "managed"—a TRI term that includes recycling, waste treatment, energy recovery, and other techniques. Again, the original industries posed the greatest problem, accounting for 31.68 billion pounds (14.37 billion kg) of managed waste, up by 34% from the 1999 total. Thus, managed and re-

leased wastes total approximately 45 billion pounds (20.4 billion kg) in the United States, or just over 160 pounds (72.6 kg) per person per year, and are increasing. Because not all industries are required to report data to the TRI, these figures underestimate the total toxic waste problem by a substantial amount.

Unfortunately, we know little about the impact of these ubiquitous wastes on human health. There are few data available that document exposure and still fewer data about the impact of these exposures on health. To fill these important gaps in knowledge and reduce risk, it is important to support health monitoring and tracking efforts and to use governmental programs

to provide incentives to move toward greener chemistry. Better health and a better environment are sure to follow.

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Response

WE APPRECIATE LOCKWOOD'S COMMENTS AND feel that there are a number of points that are important to add. We believe that it is not appropriate to include managed wastes in a metric for emissions. The chemical industry deserves credit and encouragement for the part that it has played in introducing innovative methodologies to recycle, treat, and recover by-products and energy from what were once off-site emissions. These efforts form a firm foundation for the next generation of improvements, which include green chemistry.

It is also difficult to compare raw TRI data, because over the years, the U.S. Environmental Protection Agency has made numerous changes to the rules for collecting data, such as expanding the list of reportable chemicals, lowering the reportable threshold, and changing the definition of what must be reported. Indeed, the American Chemistry

Council calculates a 65% reduction in TRI emissions during the past 12 years when these factors have been taken into account.

What is clear is that there is a significant opportunity for further improvement in achieving sustainable manufacturing and sustainable growth in an economically profitable manner. In our view, the most promising approach to these issues is green chemistry. Although it is important to understand fully the nature of our environmental problems (toxicity and exposure), we feel that it is at least as important for all members of the chemical community to engage in the ongoing discovery of the solutions to these problems. We need to remove the obstacles to implementation so that the accomplishments made thus far can be built upon for even greater environmental and economic benefit. Unrelenting effort must continue (and must be led by the industry) to reduce risk, improve our knowledge, and seek incentives to accelerate the move toward green chemistry.

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Letters to the Editor

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