Commentary on: “American Thyroid Association Guide to Investigating Thyroid Hormone Economy and Action in Rodent and Cell Models,” Bianco *et al.*

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OUR CURRENT UNDERSTANDING OF thyroid physiology and the pathophysiology of thyroid diseases is largely the result of studies utilizing animal and cellular models. These studies have led to novel diagnostic approaches and therapies relevant to clinical disease. With the currently available clinical and genetic tools, our ability to go from clinical observations to basic investigation and then back to clinical treatment is progressing at an unprecedented pace (1). Thyroid hormone transport by monocarboxylate transporter 8 (*Mct8*) has gone from characterization in basic studies, to clinical studies identifying *Mct8* gene mutations in patients with severe psychomotor retardation and abnormal thyroid function studies, to mouse models of *Mct8* mutations, and then back to clinical treatment (2,3). Mouse models of mutations in the thyroid hormone receptor (*TR*) α gene provided a range of related phenotypes suggesting how such a patient might appear (4), confirmed, at least in part, by the recent clinical characterization of two families with *TR* α gene mutations (5,6).

The greater sophistication in both basic and clinical studies to determine the many levels regulating thyroid hormone metabolism and action has highlighted the limitations translating from laboratory models to human physiology. Humans, compared with rodents, rely to a significantly greater extent on local triiodothyronine production from the type-2 5'-deiodinase enzyme, rather than the type-1 5'-deiodinase enzyme dominant in rodents (7). Mice have a higher thermoneutral temperature than humans, about 30°C (8). Metabolic studies at our usual ambient room temperature, around 21–22°C, must account for this energy expenditure made by mice to defend body temperature, or the mouse can be studied at a higher ambient temperature (9).

The report from the American Thyroid Association (ATA) Taskforce on Approaches and Strategies to Investigate Thyroid Hormone Economy and Action (10), published in this issue of *Thyroid*, provides an essential resource for thyroid investigators. Since basic research methods and experimental approaches are not generally subject to rigorous comparative studies, these are “expert” recommendations assembled by

an international panel of highly respected thyroid investigators. The universe of thyroid methods and approaches is very large, and this guide does an excellent job of identifying the core methods relevant to studies of the thyroid gland, iodine, thyroid hormone action, and metabolism, arranged in a logical and accessible format of 70 recommendations. Newer areas, including studies of thyroid hormone transport, thyroid hormone analogs, and whole genome sequencing, are included. This guide does not provide detailed protocols for the methods discussed, but instead provides recommendations linked to an extensive list of references, 725 in all. A number of figures and illustrations, a large fraction unique to this publication, complement the areas discussed. Those images illustrating rodent neck anatomy, imaging, and surgery are especially helpful and not likely to be found in most published articles that utilize these methods.

This guide will provide an excellent foundation to promote more uniformity across the many methods and approaches being used in thyroid research. It could also provide a hub for feedback, modifications, and additions, even before the usual updating that occurs with such recommendations. Presenting the guide in a format that would encourage section-specific postings and dialog, perhaps links to more detailed protocols and images, would facilitate this interaction. The launch of the new ATA publication, *VideoEndocrinology*, provides another potential bridge from this basic methods guide to videos of techniques, such as rodent surgery.

What gaps remain in information needed for the basic thyroid researchers that could receive similar attention? Techniques and reagents essential for thyroid cancer research are mentioned for a few of the recommendations, but not discussed extensively. Unique features relevant to the rapidly growing area of thyroid cancer research include thyroid cancer cell line origin, generation of primary cell cultures from thyroid cancer specimens, genetic and xenograft rodent models, surgical specimen storage and laser microdissection, and mapping of signal transduction pathways. Another broad area not specifically covered by the guide is the spectrum of rodent genetic models for thyroid diseases. Important topics in this

area include the relative benefit and limitations of the various genetic approaches (transgenic, gene knockout, and introduced mutations), cataloging the characteristics of existing models, and developing a searchable database. These would include the many models targeting genes involved in thyroid hormone synthesis, regulation, transport, metabolism, nuclear action, as well as models of thyroid autoimmunity. The likely success of this basic guide could lead to similar approaches for these other scientific areas as well as recommendations for clinical thyroid research. In this context, approaches to genetic studies and genome-wide association would be critical.

This important step towards standardizing methods and protocols in thyroid research raises the issue of access to the various reagents, antibodies, cell lines, and animal models to pursue these approaches. A significant number are available commercially for purchase, but others are not. In most cases, accepting federal research funds requires agreement to make generated resources, including model organisms, available to other researchers for noncommercial use (www.nih.gov/science/models). Although most scientists agree in principle with this policy, the cost, timing, and logistics of such sharing make it a complex issue. Many scientific societies and journals have endorsed this requirement, which may be something the ATA and *Thyroid* will consider in the future. There are existing repositories that will store and distribute select bioreagents. A thyroid-themed approach could promote storage and exchange of reagents, linking thyroid investigators as well as providing information on existing resources for sharing.

How will this guide impact thyroid research? As stated by the authors, the most significant impact should be greater uniformity and reproducibility of methods used in basic thyroid research. There should be greater recognition of the limitations of some approaches and especially a better appreciation of the appropriate application of the findings to human diseases. This guide should also serve to encourage investigators not regularly involved in thyroid research to consider, for example, evaluating thyroid status or perhaps thyroid hormone action in their system. A barrier for some has been the complexity of thyroid manipulations, which should now be much easier to standardize. It will also be helpful to have uniform recommendations that can then be tested in a wider number of paradigms and models. The success of this guide should encourage sponsorship in other areas of thyroid-related research. Perhaps, most importantly, this guide will promote greater interaction among investigators, sharing of approaches and resources, ultimately leading to expansion and progress of basic and translational thyroid research.

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