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Translational research in the decade of discovery

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Over the past three years, translational research has increasingly become a focus of interest at the National Institutes of Health (NIH). The NIH Roadmap has as one of its largest projects the new Clinical and Translational Science Awards, creating a home for translational research in academic health centers (http://nihroadmap.nih.gov). The Neuroscience Blueprint, a collaborative effort of the neuroscience institutes at NIH, identifies training in translational science as one of its major goals (http://neuroscienceblueprint.nih.gov). And the National Institute of Mental Health (NIMH) has reorganized its extramural funding programs to promote two new divisions in adult and pediatric translational research. Although translating basic science into biomarkers and new treatments for disease has always been a focus for the NIH, this renewed emphasis on translation emerges from a sense of unprecedented opportunities, opportunities that have already altered our approaches to the nation's three largest sources of mortality: cancer, heart disease, and stroke. This special issue of Hormones and Behavior demonstrates that in neuroendocrinology there are many opportunities to bridge basic and clinical research. Of course, this bridge requires strong support on both sides.

As 1990–2000 was proclaimed the Decade of the Brain, the decade of 2000–2010 may ultimately be recognized as the Decade of Discovery. In the current decade, we are in a discovery phase, finding many of the key genes and proteins critical for cellular function. This discovery phase has been powered by tools for high-throughput genotyping, broad transcriptional profiling, and comprehensive protein arrays that allow a pluralistic approach to cell biology that is quite distinct from traditional hypothesis-driven science. These tools are giving us new candidates, many of which appear critical but were simply overlooked in our focus on known proteins. This is true in neuroendocrinology as much as in cell biology. Just a few of the relevant proteins that have been discovered include GPR30, a membrane-bound receptor for estrogen (Bologa et al., 2006); P11, a chaperone for serotonin receptors (Svenningsson et al., 2006); and "an expanding cosmos" of 200 nuclear receptor coactivators in mammalian cells (Lonard and O'Malley, 2006).

At the same time that this Decade of Discovery is transforming cell biology, we have unprecedented traction in clinical research. Much of this stems from developments in two technologies: genomics and imaging. Genomics, especially the completion of the HapMap (International HapMap Consortium, 2005), has provided the tools for mapping human variation. Along with the decreasing cost for genotyping, we have an unprecedented opportunity to study how genomic variation confers risk or resilience. Indeed, as Sydney Brenner noted in his Nobel Lecture, humans are increasingly becoming a preferred "model organism" for biology, yielding opportunities for discovering new genes and new variations in known genes that may be critical for normal and abnormal function, which then can be validated in experiments in other organisms (Brenner, 2002).

For neuroendocrinology, brain imaging will also bring discoveries from clinical research. Over the past five years, increases in spatial resolution have identified regional differences in brain structure, allowing precise and longitudinal comparisons of brain development across gender or during periods of endocrine change, such as puberty (Giedd et al., 2006). Concomitant increases in temporal resolution have made possible functional studies of the neural circuits underlying the human sexual response (Ferretti et al., 2005), estrogen's behavioral effects (Goldstein et al., 2005), and individual differences in the fear response (Etkin et al., 2004).

The challenge for the next decade will be building the bridge between these revolutions in cell biology and clinical research. The traditional notion of translational research as moving from "bench to bedside" is clearly outdated. With the advent of genomics and imaging, breakthroughs are likely to emerge increasingly from research that translates from "bedside to bench." But a question raised from either side of the benchbedside continuum is, "Why bother?" The translational boundary not only is an uncomfortable no-man's land for many study sections, but also is outside the comfort zone for many scientists. So, why take the risk?

For the clinical researcher who discovers a genetic variant that alters androgen responsiveness or a neuroimaging difference associated with abnormal stress responsiveness, there is the inevitable challenge of defining mechanisms. Genetic variation is detected as a statistical association and neuroimaging findings are, at best, correlational-neither identifies proximate mechanisms in a biological sense. An understanding of mechanism requires tracking effects from genes to cells to neural systems to function of the whole organism (e.g., behavior). This is done best in organisms where each stage of this pathway can be experimentally manipulated. While nonhuman organisms, from C. elegans to mice, may not provide models of human disease, they allow the elucidation of fundamental principles, explaining, for instance, the mechanisms of chromatin remodeling or pathways from genomic variation to phenotype.

If translation from bedside to bench offers mechanisms, what is the benefit of moving from mechanistic biology to the murky realm of clinical research? For cell biologists, there is an unprecedented chance to reduce the mortality from cancer and heart disease. For neuroendocrinologists, the link is to mental and behavioral disorders. The World Health Organization names the top five sources of medical disability for Americans between ages 18 and 44 as depression, alcohol abuse, drug addiction, bipolar disorder, and schizophrenia (WHO, 2002). Major depressive disorder, a brain disease involving abnormal neuroendocrine function, affects 6.6% of the adult population (roughly 14 million Americans) each year (Kessler et al., 2003). Depression, along with other mood disorders such as bipolar disorder, contributes to the 30,000 suicides each year in this country, almost twice the number of homicides (Goldsmith et al., 2002). Endocrine transitions, from puberty to pregnancy to menopause, are the high-water marks for risk of depression and many other forms of psychopathology, but we still know very little about the mechanisms that link hormones to emotional dysregulation.

Neuroendocrinology also can inform the diagnosis and treatment of drug and alcohol addiction, by identifying the families of neuropeptides that interact with monoamines to regulate the brain's centers for motivation. Explaining the benefits and the urgent need for translation is actually the easy part. One only needs to survey recent advances achieved by bridging cell biology and cancer research. But mental and behavioral disorders have only recently been identified as brain disorders. The "basic science" of psychiatry has been, until recently, psychodynamic theory with a little neurochemistry added in the past few years. Unlike other areas of medicine, there is not a long tradition of bridging biology and clinical research for mental disorders. But the public health need for mental illness is as great as in any area of medicine. And the opportunity right now may be even greater.

This special issue of Hormones and Behavior demonstrates several opportunities for translation. It also shows the power of bringing together investigators with different perspectives to think about a common problem. It may well be that the current Decade of Discovery will give birth to a Decade of Translation. If so, this issue gives hope that neuroendocrinology will play a prominent role in bridging biology to public health.

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