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COMMENTARY

The Common Fund Initiative and Its Implication for Advancing Exercise and Physical Activity Research in Child Health

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On June 11, 2015, National Institutes of Health (NIH) Director Francis Collins announced a transformative new NIH Common Fund (https://commonfund.nih.gov/index) initiative to support research that would "lay the foundation for our understanding of how physical activity affects the human body, and ultimately, advance our understanding of how activity improves and preserves health." A particularly exciting component of the exercise Common Fund initiative was the specific mandate that, *"To ensure that the results from this program will apply to people broadly, participants in the study will range from children to older adults; include a variety of fitness levels, racial, and ethnic groups; and be equally distributed between males and females."* Implicit in this statement was an understanding of two basic concepts: first, that physical activity in children is not merely play but rather an essential component of healthy growth and development; and second, a recognition of the pediatric origins of adult disease, particularly those mediated by lifestyle and environmental factors. In this Commentary, we highlight how this call to action could ignite child health research focused on physical activity and exercise.

Established in 2006, the NIH Common Fund initiatives encourage collaboration across the NIH institutes and centers (e.g., National Institutes of Arthritis, Musculoskeletal Disease or National Institute of Child Health and Human Development) while providing the NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has been used to support a series of short-term, exceptionally high-impact, trans-NIH programs ranging from epigenomics to nanomedicine. The new physical activity initiative was stimulated, in part, by an NIH convened Workshop, *Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits* that was held in October 2014 and led to a recent publication in the journal *Cell and Metabolism (23)*. A key research effort of the Common Fund will be to support studies that gauge the impact of physical fitness and exercise training on molecular biomarkers in human populations. Specifically, as noted in the Cell and Metabolism publication, "*The incorporation of mechanistic approaches into physical activity clinical trials will require 1) establishing a infrastructure of clinical trial sites with expertise in exercise physiology, sufficient specialized exercise equipment, and standardization of protocols, and 2) populating subsets of those sites with the specialized analytic equipment, technical expertise and quality control standards needed to incorporate mechanistic outcome measures into adequately sized clinical trials.*"

The Common Fund initiative was fortuitously preceded by a recent publication that summarized the findings and recommendations of the Data Harmonization in Pediatric Exercise working group (3). This NIH-funded effort brought together scientists and clinicians from around the world and outlined the "disruptive-innovative" next steps that could exponentially advance the field. Several of the recommendations are particularly relevant to the Common Fund initiative:

- Create a network of child health focused clinical and research exercise laboratories with the ultimate goal of establishing a data consortium. The network (PEN—Pediatric Exercise Network) will:
- Work to establish robust reference values in child health cardiopulmonary exercise tests (CPET)
- Begin to more precisely define the impact of disease and therapy on exercise responses during growth and development in children
- Engage and collaborate with existing child health and adult exercise focused groups and organizations to support lifespan research, global health initiatives, and create economies of scale in the data harmonization efforts
- Use the network to establish common protocols for CPET to ensure, in particular, that data obtained from multicenter trials are truly comparable

Our challenge now is to enact these recommendations and create a robust infrastructure among the

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community of child health exercise and physical activity researchers in anticipation of engagement in the Common Fund initiative.

Leading the Way in Ideas and Concepts: Child Health Exercise Researchers are Not Just Miniature Adult Scientists

Just as we have succeeded in enlightening the biomedical research community that children are not just miniature adults, so must we highlight the novel conceptual and methodological approaches that child health and developmental translational scientists can bring to the Common Fund exercise initiative. There are at least three unique themes that must be emphasized: 1) physical activity and disrupting cellular homeostasis during dynamic periods of growth and development; 2) exercise, physical activity, and pediatric origins of adult disease; and 3) child health-focused exercise testing and biomarker discovery.

Physical Activity and Disrupting Cellular Homeostasis During Dynamic Periods of Growth and Development

As postulated by Neufer et al. (23), advances in understanding the molecular mechanisms responsible for health benefits of exercise will likely be based on the premise that *"physical activity challenges homeostasis in virtually every organ system and activates acute and long-term compensatory mechanisms to preserve and/or re-establish homeostasis."* At the core of this notion is the idea that disruptions of energy balance are pivotal in eliciting metabolic, hormonal, and (more recently) epigenetic responses that are geared to defend homeostasis. Defending cellular homeostasis during exercise is a dynamic and multifaceted process. In the acute stages this involves mechanisms that can rapidly increase oxygen delivery to the working muscle without disrupting blood and nutrient flow to the brain; activate systemic buffering pathways that limit pH changes caused by elevated anaerobic metabolism and associated acidosis; and regulate the thermal impact of the considerable heat generated by exercising muscle.

But it is the later stages of the homeostatic response, those that involve tissue plasticity, that are of particular interest to child health researchers. A remarkable facet of the human being's ability to respond to acute bouts of exercise is in the activation of longer-term adaptive mechanisms that are designed to render subsequent bouts of exercise less disruptive. The "training effect" involves changes in muscle architecture, blood supply, and mitochondrial density, and is orchestrated in many cases by the very same factors [e.g., the growth hormone®insulin-like growth factor-I axis systemically (7,11); mTOR activation at the cellular level (4,16)] that play pivotal roles in growth and development.

The impact of exercise on tissue plasticity in the context of the growing infant, toddler, child, or teen has been largely unexplored. The Common Fund Initiative, with its emphasis on molecular mechanisms, can provide an unprecedented opportunity to explore the role of exercise and physical activity during "critical periods of growth and development" (6), when environmental perturbations during brief intervals can affect growth and health across the lifespan. We can address in humans (and using animal or cellular models) central clinical issues of modern pediatrics, such as the impact of physical activity on energy balance during compensatory or catch-growth (21) in children who have suffered severe disease postnatally [e.g., survivors of congenital heart disease (2), malignancies (19), cerebral palsy (9), or psychosocial growth impairment (22)], or whether levels of physical activity can be optimized for newborns with intrauterine growth retardation and premature birth, a common cause of growth impairment (26). Finally, we can begin to better understand the molecular mechanisms that link physical activity with cognitive development in the growing child (15).

Exercise and Pediatric Origins of Adult Disease—A Use Case Example

Increasing attention has been paid to the concept that many adult diseases, particularly with regard to adult bone diseases (such as osteoporosis) and metabolic and cardiovascular conditions (such as atherosclerosis), have their origin during childhood. It is during late childhood and adolescence that exercise has been shown to be most effective in increasing bone mineral content (13,20). Evidence demonstrating the importance of exercise for lifelong bone health during this critical period is mounting; however, the molecular/cellular mechanisms involved remain enigmatic. Uncovering these mechanisms, and how they can be exploited later in adulthood to prevent osteoporosis, often a debilitating disease (28), would be a particularly compelling theme of Common Fund research.

Prevention of adult cardiovascular disease using exercise during childhood could also be a major research focus. In 2011 the American Academy of Pediatrics (AAP) and NHLBI (National Heart and Blood Institute) published guidelines (1) for cholesterol and lipid screening for children (aged 9–11) and young adults (17–21). The guidelines were a bold step in the translation of the biologic concept of pediatric origins of adult cardiovascular disease (14) to clinical implementation and disease prevention.

The evidence-based interventions recommended by NHLBI and AAP invariably involved a physical activity component (18,29). Despite the mechanistic and clinical importance of physical fitness and exercise in reducing cardiovascular disease risk, the guidelines included no recommendations to measure either of these factors, perhaps because physical-fitness and habitual physical activity biomarkers were insufficiently robust at that time to be used in primary care guidelines. The Common Fund Initiative may open doors to a molecular, genomic,

and/or epigenetic insights that can guide the clinical use of exercise in children and adolescents that can prevent adult cardiovascular disease. We now know, for example, that brief exercise alters gene and microRNA profiles in circulating leukocytes in both children and adults (24,25). Perhaps additional epigenetic processes may shed light on how the immune system can be programmed (27) during childhood to favor health over disease.

Child Health Focused Exercise Testing and Biomarker Discovery

Although the details of the Common Fund scope are not yet available, it is clear from the initial press releases and the workshop summary (23) that prospective studies involving exercise training will be emphasized. Multicenter trials will likely be needed to power mechanistic and biomarker discovery studies appropriately. Implementing key practices of "team science" (12), data interoperability, and terminology harmonization will be essential for the success of the initiatives. Child health researchers have led the scientific community in identifying ways to coalesce creative informatics approaches in multisite research (17), and in the creation of networks that integrate generalists and specialists that have immeasurably advanced child health in many areas (30).

The ambitious goals of the Common Fund initiative demand an unprecedented degree of creative consensus building in quantifying the elusive physiological phenotype that emerges from CPET, strength testing, muscle function metrics, and field assessments of fitness in children and adolescents. Ongoing promising activities include novel ways in which we can more fully use the data obtained from exercise testing in children (8) and employing ubiquitous computing to assess physical activity in the real lives of children (5). Finally, tied to any successful intervention will be innovative use of behavioral science in understanding how best to motivate children and adolescents to participate in exercise training programs with optimal fidelity (10).

Summary

NIH Director Francis Collins noted that the Common Fund initiative would lead to unprecedented insights into the mechanisms responsible for the health effects of physical activity. He noted: "Armed with this knowledge, researchers and clinicians may one day be able to define optimal physical activity recommendations for people at various stages of life, as well as develop precisely targeted regimens for individuals with particular health needs." Given the ominous burden of physical inactivity-related diseases and conditions in otherwise healthy children, and the growing number of children who survive chronic diseases in whom we know little about what constitutes healthy exercise, it is essential that the community of child health researchers develop compelling strategies and proposals in response to the unique opportunity offered through the Common Fund mechanism.

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