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Exercise Biology and Medicine: Innovative Research to Improve Global Health

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The purpose of this Commentary is to emphasize the powerful impact rigorous, interdisciplinary exercise medicine research can have on clinical practice and public health policy. Because exercise profoundly influences virtually all aspects of human biology, research on dose-response relationships, exercise-drug/device interactions, exercise genomics, personalized medicine, disease and population specificity, and behavioral medicine offers enormous potential for novel insights into health and disease. With this core concept in mind, here we: (i) briefly summarize the opposing powers of exercise and chronic inactivity; and (ii) discuss the decided advantages of innovative exercise research to advance translational science and ultimately global health.

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Exercise vs. Inactivity: Powerful, Opposing Forces that Modulate Health Across the Lifespan

Over the last 100 years the science of exercise has grown from seminal discoveries demonstrating the effects of exercise intensity on vascular control, heat production, oxygen requirement, and lactic acid dynamics – which led to Nobel Prizes in Physiology or Medicine in 1920 (August Krogh, Denmark) and 1922 (A.V. Hill, Britain, and Otto Meyerhof, Germany) – to our modern-day understanding that one's cardiorespiratory fitness (CRF) (indexed by one's maximum rate of oxygen consumption, VO_2max) is among the most powerful predictors of morbidity and mortality.¹⁻³

Exercise training – regularly performed, prescriptive, dose titratable physical activity – is increasingly used as an adjuvant therapy across a wide range of human diseases consequent to now documented improvements in cardiac function, muscle oxidative capacity, metabolic health, glucose and lipid homeostasis, adiposity, inflammatory burden, muscle mass and strength, joint pain, mobility function, depression, anxiety, and cognition^{4, 5} (Figure 1). On the other hand, the evidence is now incontrovertible that poor fitness and low physical activity are major causes of chronic, non-communicable diseases (CNCDS) – e.g., heart disease, stroke, type 2 diabetes, chronic respiratory diseases, and some cancers – which account for approximately 60% of deaths worldwide.⁶⁻⁹ The economic burden attributed to CNCDS reaches hundreds of billions annually in lost productivity and healthcare expenditures; yet, ironically, the bulk of CNCDS-related morbidity and mortality is preventable.^{6, 9}

Taking Advantage of Exercise Research to Advance Translational Science

While there is general consensus that exercise is integral to the prevention and treatment of chronic disease (i.e. “exercise is medicine”¹⁰), the field is ideally positioned for innovative research that would bolster current efforts to transform the translational research enterprise¹¹ by addressing key knowledge gaps.

Discovering new molecules and pathways

Exercise activates a complex array of coordinated cellular and molecular processes involving a wide array of signaling networks and transcriptional regulators that differentially affect virtually every human tissue and organ system¹². As such, even a single exercise bout can be used experimentally as a quantifiable, reproducible perturbation to cellular homeostasis (Figure 1A) that may well reveal novel mechanisms regulating biological adaptations to long-term exercise training (Figure 1B) that prevent or manage disease. Taking advantage of exercise potency for such discovery purposes is exemplified by the seminal 2012 discovery that exercise-induced autophagy plays a key role in glucose homeostasis and is largely controlled by B-cell lymphoma 2 (BCL2)¹³. Moreover, researchers in the exercise field have been largely responsible for the recent discoveries that skeletal muscle is an endocrine organ, that secretion of growth factors and novel myokines is sensitive to the level of contractile activity, and that exercise-induced myokine secretion may play important disease-fighting roles¹⁴⁻¹⁶. This area is ripe for future research expected to contribute enormously to the translation of science into real benefit for humans.

Exercise-drug/device interactions

It is important to consider levels of physical activity and carefully evaluate disease-specific exercise interventions prior to medication usage, and certainly as an integral component in the development and evaluation of any drug or device therapy. There is a solid rationale for such a strategy, particularly considering that a lifestyle intervention (i.e. moderate intensity

physical activity combined with a reduced calorie diet) out-performed metformin in a large population of obese individuals at risk for type 2 diabetes, and the benefits of physical activity + diet (vs. metformin) were actually underestimated due to intent-to-treat analysis¹⁷. The United States Food and Drug Administration (FDA) seems to concur with this approach. In its draft guidance document released in 2007 for industry developing weight loss drugs, the FDA recommended that “the use of weight-management products should be contemplated only after a sufficient trial of lifestyle modification (diet and exercise) has failed.”¹⁸ Furthermore, the FDA recommended that Phase 3 trials for weight loss products be conducted with a lifestyle modification as the “placebo” condition.¹⁸ In our view this approach should prevail throughout all phases of drug/device development including the pre-clinical studies in laboratory animals. The sedentary, overfed state of typical laboratory mice and rats leads to obesity, metabolic syndrome, and early mortality compared to counterparts in the wild, raising the question of whether this “couch potato” state of caged laboratory animals is an appropriate control condition since its profound effects may skew and even mislead drug efficacy results.¹⁹ On the other hand, for some applications one could argue that this is a realistic pre-clinical model based on the current prevalence of obesity and sedentary behavior among U.S. adults and children.

Exercise can profoundly influence drug pharmacokinetics²⁰; thus there is a need for adjunct exercise + drug testing to determine if exercise training enhances or interferes with drug outcomes, or vice versa. For example, in HIV+ patients with insulin resistance and central adiposity, exercise training enhanced the insulin sensitizing effects of pioglitazone.²¹ On the other hand, 40 mg/d simvastatin completely abrogated beneficial endurance exercise training adaptations including enhanced CRF and skeletal muscle mitochondrial function.²² Exercise performance can also serve as a valuable biomarker of drug/device efficacy. For example, among heart failure patients, the acute heart rate response to a single bout of moderate exercise is a valuable, independent predictor of failure to respond appropriately to cardiac resynchronization therapy.²³ The popular understanding that exercise improves health is reflected (albeit, often with damaging hyperbole) in media attention given to exercise discoveries that attract some to suggest that single-target drugs can mimic the complex, multi-system effects of actual exercise training (Figure 1). Clearly there is no single mediator capable of recapitulating all of the physiological adaptations to exercise and assertions that promote “exercise pills”²⁴ are misleading. On the other hand, exercise research can very effectively inform and perhaps expedite the search for medicines that enhance the benefits of physical activity in patients with physical (e.g., mobility impairment^{25, 26}) or physiological (e.g. abnormal pressor responses^{27, 28}) constraints that otherwise limit exercise tolerance and thus prescription options.

Drug repurposing

Exercise fits into the overall public health interests of lower cost, readily available therapies, and should be considered within the context of primary prevention, cure acceleration, and drug development. In the U.S., for example, it is an average of 14 years from target discovery to FDA approval of a new drug, failure rate exceeds 95 percent, and the cost per successful drug is more than \$1 billion, after adjusting for all of the failures.¹¹ Inclusion of exercise as a comparator or adjunct therapy in pre-clinical and clinical efficacy studies would likely streamline the process and ensure that the outcomes are translatable.

A major research priority in translational science is to expedite the time to effective cures or disease management by finding new, alternative uses of currently approved medications. Exercise can and should be used as a powerful tool in this process, as exemplified by the elegant, pre-clinical work of Srinivasan et al.²⁹ In their search for effective ways to prevent osteoporosis, these investigators found that supplementing exercise-mediated mechanical loading with low-dose cyclosporin A completely rescued loading-induced bone formation in

the aged skeleton. One can envision capitalizing on any number of putative as well as novel physiological adaptations to specific modes of exercise (Figure 1) to advance drug repurposing.

Dose-response relationships and exercise genomics

Like any other treatment the desired outcomes of exercise training are highly dependent on the type and dose of the prescription and genetic variation, with substantial gaps in knowledge remaining.⁴ An individual's "trainability" – ability to adapt optimally and thus reap the full benefits of any specific exercise training prescription – is likely determined by genetic, environmental, and phenotypic factors. Molecular signatures predictive of trainability are emerging,³⁰ opening a new frontier of "exercise genomics"³¹ research that is positioned to advance personalized medicine in both prevention and therapeutics. Additionally, well-controlled exercise trials comparing doses (e.g.,³²) in a disease-specific manner are sorely needed and should take full advantage of advances in genomics, epigenetics, proteomics, metabolomics, stem cell biology, and imaging technologies to shed light on the complexity of exercise adaptation. These tools present rich opportunities for innovative and translational research.

Exercise adherence and behavioral medicine

A major challenge in the field that affects clinical application of exercise medicine among healthcare providers is a perception among many that, despite the proven benefits, adherence to unsupervised exercise prescription is poor. In addition to patient outcomes, exercise adherence rates profoundly influence hypothesis testing in the research setting.³³ The 16-center Look AHEAD trial included a number of behavioral strategies to promote adherence to an at-home lifestyle intervention (diet + moderate physical activity) in obese and overweight type 2 diabetics, and several encouraging secondary outcomes were noted in the short term.³⁴ On the other hand, the discouraging incidence (not different from education control) of cardiovascular events (primary outcome) in the long term led to early closure of Look AHEAD following a futility analysis.³⁵ While adherence to the clinic visit schedule during the first year (1-3 group meetings and 1 individual session per month) was ~80%,³⁴ it is certainly possible that variable adherence to the daily/weekly at-home diet and exercise recommendations over the long term played a significant role in the futile result. There is a remarkable need, and therefore opportunity, for interdisciplinary research in behavioral medicine to identify key factors influencing exercise adherence, as well as intervention strategies that foster lasting behavioral change. In fact, understanding inter-individual variability in exercise adherence is an emerging science, and a few genetic and non-genetic predictors of adherence have been described recently.³³

Exercise is powerful medicine

Apart from the attractive opportunities to exploit the exercise stimulus for discovery and in drug/device development, it must be emphasized that exercise itself is a proven and readily available therapy that has demonstrated a high therapeutic index in a number of disease states with little to no side effects.⁴ While the issue of adherence cannot be overlooked, the power of exercise in CNCD treatment and protection from CNCD-related morbidity and mortality is profound.⁴ In fact, in their recent synthesis of current data on the protective effects of exercise training against cardiovascular disease, Joyner and Green³⁶ demonstrated that exercise-mediated protection far exceeds the degree of protection predicted based on traditional risk factors. For example, exercise-mediated reductions in low-density lipoprotein (LDL) cholesterol or increases in high-density lipoprotein (HDL) are only modest;^{37, 38} yet risk of cardiovascular disease is reduced upwards of 50%, which rivals or exceeds the cardioprotection associated with statins³⁹ without the adverse effects. This poorly

understood “risk factor gap” shows the potency of exercise, and points to the significant opportunities for potentially pivotal exercise-related discoveries.

Today, rehabilitative approaches after surgery of various types focus heavily on early mobility and prescriptive exercise (e.g., coronary bypass⁴⁰), as opposed to prescribed long-term disuse or bed rest just a few decades ago. In fact, the success of exercise training in cardiac rehabilitation has led to the current push for insurance-sponsored prevention programs that would extend to a number of cardiometabolic disease states.⁴⁰ Beyond treatment of CNCDS, exercise prescription has shown great promise in rare and orphan diseases, which presents an enormous opportunity for future research. Pharmacological therapies clearly are a necessity for some diseases and health crises. However, for many conditions, exercise can serve as a positive behavioral and physiological modifier of the disease process. For example, myopathies such as limb-girdle muscular dystrophy,⁴¹ as well as neurodegenerative diseases (e.g., Parkinson's disease⁴²), benefit from exercise. Unfortunately data are lacking to guide exercise prescriptions for many diseases; thus large-scale (Phase 3 equivalent) research focused on dose-response efficacy would have a powerful impact.

Summary and Recommendations for Future Research

While a host of benefits are undeniable, to fully capitalize on exercise pluripotency, key knowledge gaps demand robust research in (at least) five priority areas: 1) optimizing exercise dosing in a disease or population-specific manner to streamline clinical care; 2) a better understanding of exercise-drug/device interaction, synergism, or antagonism; 3) genetic and non-genetic determinants of both exercise responsiveness and adherence, enabling personalized treatments and advances in behavioral medicine; 4) mechanisms by which physical inactivity across the lifespan fosters development and progression of CNCDS; and 5) taking advantage of the potent exercise stimulus to discover new molecular targets and potential re-purposing uses for currently available medications. In summary, we strongly recommend that exercise medicine research be embraced as a grand opportunity to advance knowledge that will help abate the global health crises driven largely by common CNCDS, and to find effective therapies for rare and neglected diseases.

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List of Abbreviations

VO₂max	maximum rate of oxygen consumption
CRF	cardiorespiratory fitness

CNCDs chronic, non-communicable diseases
FDA United States Food and Drug Administration

Figure 1A

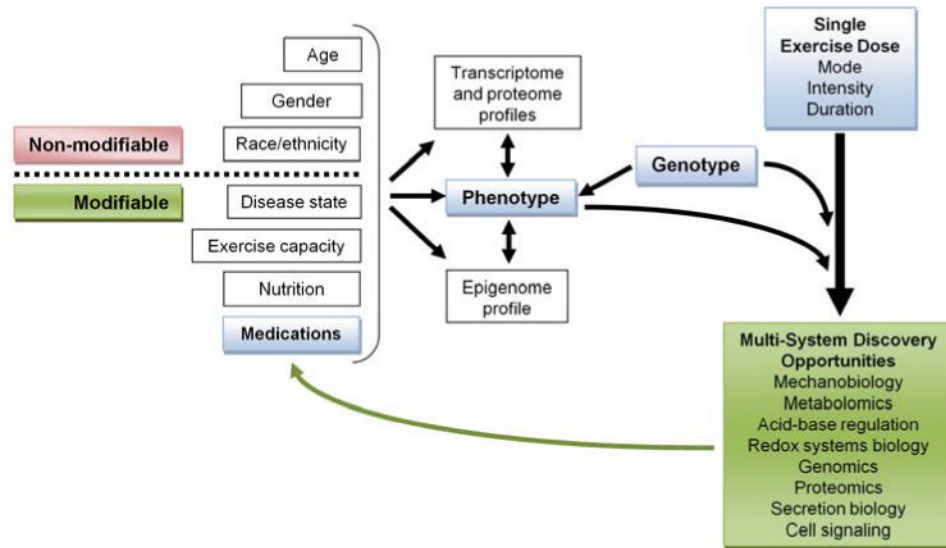


Figure 1B

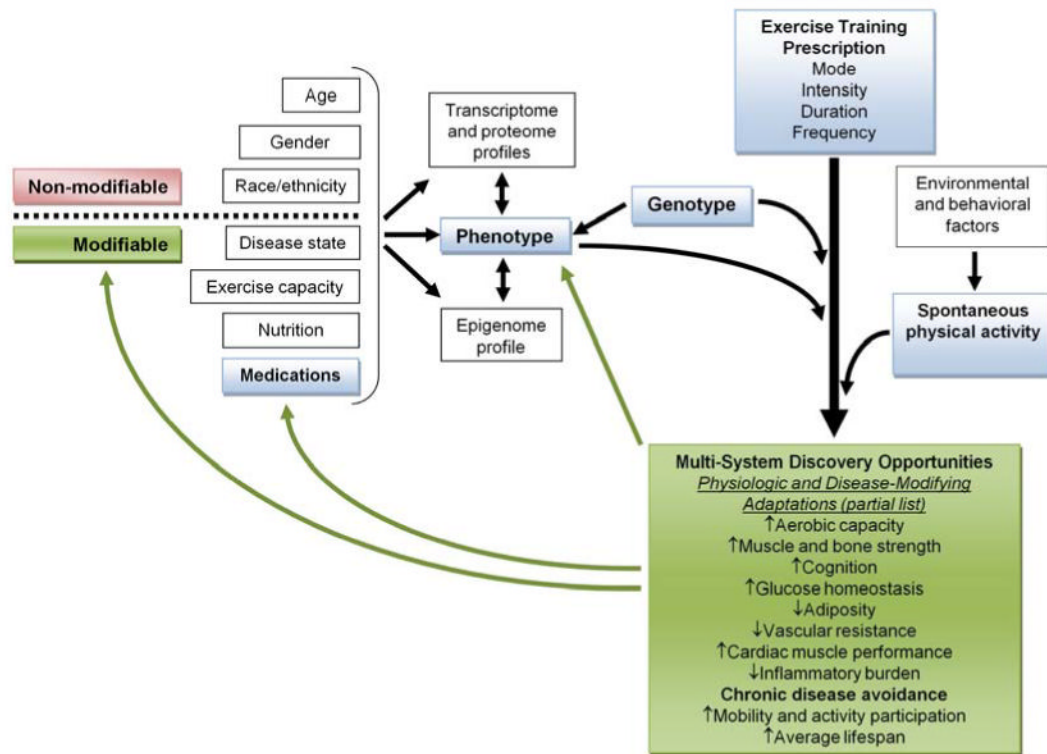


Figure 1. Discovery opportunities driven by (A) acute response exercise research, and (B) exercise training and physical activity research.