Investing in High Blood Pressure Research
A National Institutes of Health Perspective

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• Online Data Supplement

Hypertension (HTN), traditionally defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg, or currently taking medication to lower high blood pressure,1–3 is a common and chronic disease that currently affects 77 million Americans. The National Health and Nutrition Examination Survey conducted in 2009 to 2010 found an overall HTN prevalence of 28.6% in American adults aged ≥18 years.4 Prevalence increased greatly with age, ranging from 6.8% among individuals aged 18 to 39 years to 30.4% in those aged 40 to 59 years, and to 66.7% in individuals aged ≥60 years. HTN is a major risk factor for the most deadly cardiovascular diseases, preceding the development of heart failure in 91% of cases; it is present in 69% of individuals who suffer their first heart attack and in 77% of those having their first stroke.5 HTN and diabetes mellitus combined are the strongest predictors of chronic renal disease. Even prehypertension, defined as untreated systolic blood pressure of 120 to 139 mm Hg or untreated diastolic blood pressure of 80 to 89 mm Hg, is associated with elevated relative and absolute risks for cardiovascular disease outcomes, which differ by race and increase with age.6 The status of HTN severity and treatment (ie, treated or not) are both components of personal risk-estimating algorithms, such as the Framingham General Cardiovascular Risk Score,6 based on data from the National Heart, Lung, and Blood Institute (NHLBI)-sponsored, longitudinal, observational Framingham study.7 Conversely, treatment of HTN was shown to lead to reduction of cardiovascular disease complications, with benefit levels largely relating to the extent of high blood pressure lowering. Treatment of HTN often requires the use of various and sometimes concomitant medications, frequently accompanied by significant side-effects. Trials that previously targeted high systolic blood pressure demonstrated significant percent reductions in incidence of stroke (in average 35%–40%), myocardial infarction (in average 20%–25%), and heart failure (in average 50%).8 Reviews of blood pressure treatment studies in high-risk populations have prompted recent treatment guidelines9 from the European Society of Hypertension to recommend lowering systolic blood pressure to 130–139 or diastolic blood pressure to 80–89 mm Hg in an effort to reduce adverse CV events.4

More information regarding the degree to which blood pressure can be safely lowered will be forthcoming from the ongoing Systolic Blood Pressure Intervention Trial (SPRINT),10 sponsored by the NHLBI.11

HTN thus represents a formidable challenge to human health and to US healthcare, with direct expenditures estimated at $50 billion. Both the National Institutes of Health (NIH), the largest source of funding for biomedical research in the world, and the American Heart Association invest significant funds in research efforts aimed at improving understanding of the basic pathophysiology of HTN and translating findings into effective preventive strategies and therapeutic interventions. To better assess the breadth and depth of the current HTN research sponsored by the NIH, we performed surveys of the related grant portfolios funded by the NIH and NHLBI focusing on the large group of research awards administered by the Vascular Biology and Hypertension Branch (VBHB) within the NHLBI.

Methods and Results

Survey of the NIH-Sponsored HTN Research

The publicly available NIH Research Portfolio Online Reporting Tools (RePORT) provide access to estimates of annual NIH funding for various research, condition, and disease categories based on the Research, Condition, and Disease Categorization database.12 Research Portfolio Online Reporting Tools is helpful in informing the US Congress, the general public, and the research community about the scope and size of NIH investments in specific diseases. Using this tool, we analyzed the Research, Condition, and Disease Categorization funding information for the category HTN for fiscal year (FY) 2011. The total value of the current NIH investment in HTN research was estimated at $240 million. Several NIH Institutes and Centers (IC) sponsor HTN-related awards within their respective areas of interest. The relation between major NIH-sponsored research topics and their various IC can be surveyed in real time using a new online tool called the NIH Map Viewer,13 which allows distillation of information down to the level of individual awards. The landscape of HTN-related research at the time of this report is illustrated in Figure S1 in the online-only Data Supplement. Among the NIH Institutes in FY2011, the NHLBI sponsored the great majority of HTN research...
both in terms of number of awards (60%, Figure 1A) and amount of funding (62%, Figure 1B), followed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). When analyzing the types of HTN research, we found that the majority of NIH- and NHLBI-supported research fell under the basic and translational categories (Figure 2). This was true both in terms of number of awards made and amount of funding received in FY2011. The remainder of the NIH/NHLBI investment was made in clinical research and training, reflecting an overall commitment to a diverse research portfolio14 and a new generation of HTN researchers.

Awards with HTN as the major focus were supported through several types of NIH funding mechanisms.15 The predominant NHLBI research support in FY2011 was allocated to investigator-initiated research projects, known as R01s, followed by program project grants, or P01s (Figure 3). A significant investment was made in different types of training grants related to HTN. Of the NHLBI basic and translational research awards, 4% utilized R21s, accounting for 4% of total number or 2% of total funding. Exploratory/developmental research grants, or P01s (Figure 3). A significant investment also was made in different types of training grants related to HTN. Of the NHLBI basic and translational research awards, 4% utilized R21s, accounting for 4% of total number or 2% of total funding.

Gaining Further Insights About the NHLBI-Sponsored HTN Portfolio

The NHLBI allocates significant funding for research to discover underlying causal mechanisms of HTN and strategies to treat or prevent the organ damage caused by sustained HTN. To gain further insight into the nature of HTN research supported by VBHB-administered awards, we performed an in-depth portfolio analysis, examining the current major areas of research focus, the main experimental approaches used, and publication output. From this analysis, we could gauge some of the emerging scientific concepts and trends in HTN research.

We found that virtually all the awards focused on the role of the kidneys, the brain, or vasculature in the pathogenesis of HTN, and that their distribution was fairly equal (Figure 4A). In contrast, the distribution of main experimental manipulations used to induce HTN in various animal models was heavily weighted toward the use of the angiotensin (Ang) II infusion approach, which accounted for almost half of all the HTN awards (Figure 4B). Further breaking down the data by the main organ of interest, we found an overwhelming preponderance of Ang II infusion in the awards focused on the brain: 67% used Ang II infusion, 17% chronic intermittent hypoxia, and 11% used diet-induced obesity. Among projects focused on the kidney, 48% relied on inducing HTN by Ang II infusion, whereas 43% used various genetic models of HTN. Among projects focused on the vasculature, 38% used Ang II infusion, 24% used genetic models of HTN, and 14% used either diet-induced or DOCA (deoxycorticosterone acetate) salt to induce HTN. In the remaining projects in each category, the percentages using other experimental models or manipulations were in the single digits. Although the Ang II infusion method of inducing experimental HTN is very effective, a heavy reliance on it could be problematic. Testing hypotheses in multiple or new experimental models might increase fidelity of translation of experimental findings to human HTN. Of note, experimental animals used in many of these experiments, including in conjunction with Ang II infusion, had been developed by molecular targeting of specific genes.

The publication output of the VBHB research portfolio was measured as number of publications per year. These included all publications (original reports, review articles, etc.) that had acknowledged support through awards administered by our Branch. We found this number has steadily increased since 2005, consistent with the rise in the number of awards made. Dividing the total amount of funding by the total number of publications yielded an average of $150,000 in funding per publication, consistent with numbers associated with other areas of CVD investigation sponsored by NHLBI, and under the national estimates of cost per publication for all academic-based research.16 The Public Access Policy,17 which requires grantees to acknowledge their funding sources in publications, facilitates generation of reports about the impact of NIH funding. Investigator adherence to this policy not only helps advance science and improve human health by making research publications widely accessible, it also enables the NIH to justify its requests for future allocations of public funds to biomedical research.

Identifying and Fostering Emerging Trends in HTN Research

In addition to analyzing existing portfolios, we seek various ways to assess emerging trends in HTN research and anticipate potential research needs. Traditionally, the NIH staff has obtained information about knowledge gaps and understudied areas of investigation at scientific meetings and NIH-convened working groups of invited external experts. The most recent example of an HTN-related working group was organized by the VBHB to examine the potential role of epigenetics in HTN.18

Recommendations from such working groups are subjected to a multilayered internal review process that may result in development of initiatives, also known as funding opportunity announcements. These include requests for applications (RFAs), requests for proposals (RFPs), and program announcements (PAs). The funds set aside for NIH-initiated targeted research represent about 10% of the regular extramural NHLBI investment.19

One VBHB-sponsored initiative, “Cellular and Molecular Mechanisms of Arterial Stiffening and Its Relationship to Development of HTN” (RFA HL-10-027), was published in 2009,20 in response to recommendations of an external expert working group assembled by the NHLBI in June 2008 to advise regarding: “Target Organ Damage in Hypertension: Research Priorities and Infrastructure Needs.”21 The grantees of this RFA recently gathered for a second annual meeting and already reported concordant results from several experimental animal models of HTN indicating that arterial stiffening precedes HTN.
In a rare coincidence of efforts and results, investigators of another VTBH-supported, independent clinical study reported the same temporal sequence in patients of the Framingham cohort. This particular concordance solidified the direction of a potential causal relationship between arterial stiffening and HTN, and emphasized the need and opportunity to go back to the bench to investigate the specific molecular pathways by which arterial stiffening may lead to HTN.

Obtaining clinical evidence, such as the findings on arterial stiffness, which challenges our current understanding of HTN, provides new starting points and great directions for basic research. Other HTN-related clinical questions still awaiting for answers include assessing the benefit versus risk levels associated with treating low-to-moderate HTN for prevention of stroke and myocardial infarction, the effects of coexisting diseases, obesity, and multiple medications, including statins.

Other questions that might be answered more expeditiously in animal models are related to the long-term effects of new therapeutic modalities being clinically tested, such as renal denervation. We found that only a handful of NIH research grants focus on this intervention, which is already being seen as holding great promise in HTN. Other clinical information, such as that provided by genomic studies, could be tested and elucidated in experimental models. About 4% of NHLBI awards are focused on identifying single-nucleotide polymorphisms associated with HTN in humans. The role of these molecules might be elucidated, and new HTN experimental models might be developed by leveraging resources, such as those provided by the Knockout Mouse Project (KOMP), which is a comprehensive public resource comprising mouse embryonic stem cells containing a null mutation in every gene in the mouse genome (KOMP, www.komp.org). A second phase of this endeavor, the Knockout Mouse Phenotyping Project (KOMP2), has the goal of generating 5000 strains of KO mice that will undergo a large battery of phenotype tests by 2016 as those provided by the Knockout Mouse Project (KOMP), which is a comprehensive public resource comprising mouse embryonic stem cells containing a null mutation in every gene in the mouse genome (KOMP, www.komp.org). A second phase of this endeavor, the Knockout Mouse Phenotyping Project (KOMP2), has the goal of generating 5000 strains of KO mice that will undergo a large battery of phenotype tests by 2016 as those provided by the Knockout Mouse Project (KOMP), which is a comprehensive public resource comprising mouse embryonic stem cells containing a null mutation in every gene in the mouse genome (KOMP, www.komp.org).

Another question is whether the genes of interest are already in the public domain. Investigators can leverage newfound HTN treatment, obesity, oxidative stress, pregnancy, reactive oxygen species, and salt sensitivity.

**Discussion**

**Increasing Public Awareness About the Risks of HTN, Importance of HTN Research, and Societal Benefits of Science**

The NHLBI coordinates with the National High Blood Pressure Education Program, which relies on a cooperative effort among professional and voluntary health agencies, state health departments, and many community groups to raise awareness and educate the public about HTN. In spite of the high healthcare expenditures related to treating HTN, recent data indicate that the previous trend of increasing public awareness regarding the risks of HTN is reversing. This alarming trend makes it imperative that researchers increase the public awareness about the risks of HTN and the importance of continuing to support biomedical research. Several recent surveys indicate that the value of scientific research for the society as a whole is not necessarily apparent to the public. This issue is even more urgent in the current challenging fiscal climate. Opinion polls
conducted by independent agencies soliciting suggestions for decreasing the deficit found that many suggested cutting investments in science and technology, although these investments account for a relatively small percentage of the US budget. Also, the investment in biomedical research represents only 4.5% of total healthcare costs. Yet, NIH awards directly fuel the US economy, creating jobs in our communities. In FY2011, NIH research funding supported an estimated 432,000 US jobs at >2500 universities. Every dollar of NIH funding generated about $2.21 in local economic growth. Appreciation for the value of science and scientists’ contributions could be increased if scientists clearly and consistently explained the rationale and potential impact of their own research to wider audiences. Such communication skills need to be encouraged and honed and become part of every scientist’s tool box. Relevant exercises could be built into regular scientific activities or training programs. Several universities have dedicated science communication programs and courses, but free resources to get started are available online, including via the Center for Public Engagement with Science and Technology of the Advancing Science, Serving Society or YouTube.

This year was particularly successful for the cardiovascular sciences, with 3 previous or current NHLBI grantees being awarded the Nobel Prize. These researchers joined the distinguished ranks of >200 NIH supported researchers who received Lasker awards and well >100 who won Nobel Prizes. Two of this year’s laureates, Robert J. Lefkowitz, MD and Brian K. Kobilka, MD, made important basic scientific contributions to the field of G-protein–coupled receptors, which are targeted by >40% of currently used therapeutic agents. Their work specifically led to the development of β-adrenergic receptor blockers used to treat HTN, angina, and coronary heart disease. This recent major success further highlighted the importance of supporting basic research as a basis for major scientific and public health advances, a tenet of NIH mission. Similar great discoveries have also contributed to the steady increase in life expectancy in the United States, with 70% directly attributable to the reduction in death from cardiovascular disease.
The basic understanding and clinical management of HTN have advanced, yet the remaining disease burden demands continued dedicated research, public health efforts, and investments through partnerships with the research community, patient advocates, and government agencies. The NIH is committed to helping the HTN research community by identifying challenges and opportunities, and continuing to stimulate and enable innovative HTN research.

Acknowledgments
We thank Drs Larry Fine, Eser Tolunay, Cheryl McDonald, and Paul Velletri of the National Heart, Lung, and Blood Institute for helpful suggestions for the article, and Kelin Fuentes for her assistance with formatting references and text editing.

Sources of Funding
All authors are employees of the National Heart, Lung, and Blood Institute. No specific funding was allocated for this work.

Disclosures
None.

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Online Supplement

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Figure S1. Landscape of HTN-research falling within various main scientific areas sponsored by several NIH institutes. This image was generated by the “NIH Map viewer” (app.nihmaps.org) using the search term “hypertension” on the date of writing the report (Oct 2012)

Figure S2. Term clouds generated by analyzing the text (specific aims) of all HTN-related grants funded by the NIH in FY2008 and FY2011. Grants were identified by RCDC categorization. Font weights reflect the frequency with which those terms appear among the awards.