On the Value of Portfolio Diversity in Heart, Lung, and Blood Research

In his widely acclaimed book "The Difference" (1), Scott Page, a Professor at the University of Michigan, described a computer modeling experiment designed to test the "Diversity Trumps Ability Theorem." The theorem postulates that "collections of diverse individuals outperform collections of more individually capable individuals" (1). The computer model showed that diversity enhanced the ability to solve problems or make accurate predictions (2), but only when 4 conditions were met: (*1*) the problems were difficult, (*2*) all problem solvers were "smart" (but not the smartest), (*3*) diversity was sufficient to ensure that different problem solvers could exploit the solutions of others, and (*4*) the populations of problem solvers and collections of problem solvers were large (1). As all 4 of these conditions are clearly met in heart, lung, and blood (HLB) research, we were stimulated to examine the diversity of topics and mechanisms in the National Heart, Lung, and Blood Institute (NHLBI) portfolio.

To further support his argument for the benefits of diversity, Page cited a number of empirical examples, including cities (3), policy-making agencies, management teams, and groups of scientists (1). Other authors have cited examples supporting the importance of diversity in science: multidisciplinary interactions have repeatedly been shown to generate greater degrees of rigor, creativity, evolution of ideas, academic productivity (4), and innovation (5, 6). Page argues that when faced with difficult problems, different people (or more generally different agents) can bring different "toolboxes." Diverse toolboxes offer varying perspectives, interpretations, heuristics, and prediction models. Diversity works, both theoretically and empirically, because application of many different toolboxes reframes confusing data into eminently solvable problems and because diverse agents naturally build upon each others' work (1, 2).

Science is one of society's most valuable diverse "toolboxes" for improving health and for serving as a sound economic investment (7). Over the past 60 years, diverse groups of government-funded researchers in basic, translational, clinical, and epidemiological sciences played pivotal roles in enabling dramatic reductions in cardiovascular mortality and morbidity (8). Research America reports that every million dollars invested by the National Institutes of Health (NIH) generates 2 millions of new state business activity (9). Yet, the value of a diverse biomedical science toolbox, funded through an investment that is relatively small given the nation's total health expenditures (about 1 penny for each dollar) (9–11), is questioned by some, with concerns being raised about what constitutes "worthy" science or wasteful projects (12). Others criticize funding agencies for being too conservative or spending too much in specific areas (13). Some scientific thought leaders have even called into question the value of funding research projects outside their own spheres or expertise (13–16). Unfortunately, there is no simple and universally accepted approach for allocating finite research resources (17). In fact, many of the arguments being heard today were also raised 20 years ago in another period of budgetary constraint (18).

Not surprisingly, whenever the economic landscape forces limitations on research funding, organizations that support science engage in a cyclic "soul searching" exercise. They face choices regarding types of science to fund (basic, clinical/applied), levels of risk to assume ("sure bet" versus high risk/high reward), sizes of awards, and distributions among different types of applicants (individuals and/or large teams). The NIH recently invited the scientific community to provide input on "*How Do You Think We Should Manage Science in Fiscally Challenging Times?*" (19).

The NIH has long supported a diverse, balanced mix of basic and applied research. The basic-to-applied funding ratio has remained remarkably constant: in 1994, 57% of NIH research funding supported basic research, whereas 43% supported applied and development research. In 2004, the corresponding values were 55% and 45% (20), whereas more recently they were 56% and 41% (21). Even with the formation of the new National Center for Advancing Translational Sciences (NCATS), NIH remains publicly committed to maintaining that traditional balance (22, 23).

Just as in other fields, scientific diversity has been and continues to be critical for the success of HLB research. What do we mean by scientific diversity? Stirling cites three parameters: variety, which refers to the number of categories; balance, which indicates "how many of each"; and disparity, which describes how well categories can be distinguished (5). As with other natural or man-made environments, the survival, evolution, and eventual success of scientific ecosystems depend on their ability to capitalize on diversity in variety, balance, and disparity, especially under challenging conditions. For instance, it has been argued that the driving forces in the growth and development of cities and regions can be found in the productivity gains associated with the clustering of a diversity of talented people (human capital) (3).

Schneider (24) offers a different construct, proposing that scientists come in 4 "flavors," all of which are essential for moving any scientific field forward. The scientists of the first flavor excel at being able to visualize the "fuzzy front end." Their out-of-the box ideas are then translated into doable experiments designed and executed by scientists of the second and third flavors. Their experiments allow the new ideas to be methodically tested and then synthesized and further developed into new hypotheses by the fourth flavor of scientists who collect, categorize, interpret, and pass on large amounts of data. Schneider's categorization may be oversimplified, but it illustrates how biomedical science is a relay exercise, better, a collection of relay exercises, by which scientists (better groups of scientists), interact to solve the many complex problems presented by human health and disease. As a community, we are most successful when we achieve active engagement of diverse problem solvers, including basic scientists, engineers, translational and clinical researchers, clinical practitioners, statisticians, policy experts, patients, communities, and indeed all

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TABLE 1. FISCAL YEAR 2010 EXTRAMURAL NHLBI PROJECTS BY SELECTED MECHANISMS THAT TOGETHER ACCOUNTED FOR 87% OF ALL EXTRAMURAL FUNDS

	Nonclinical Projects			Clinical Projects		
Mechanism	No.	Total Funding (% Extramural Funding)	Median Cost per Project (25th, 75th Percentiles)	No.	Total Funding (% Extramural Funding)	Median Cost per Project (25th and 75th Percentiles)
Contract	86	155,399 (6%)	1,717 (522, 2,274)	68	65,479 (3%)	378 (109, 1,018)
P01	120	187,232 (7%)	1,752 (1,018, 2,116)	33	57,204 (2%)	1945 (1,570, 2,423)
P50	1	1734 (<1%)	—	21	42,449 (2%)	2247 (1,619, 2,594)
R01	2475	804,079 (33%)	381 (364, 410)	995	515,239 (21%)	431 (375, 672)
R21	263	37,610 (2%)	213 (191, 231)	71	14,664 (<1%)	199 (189, 228)
R44	50	27,958 (1%)	500 (373, 681)	34	26,727 (1%)	647 (420, 998)
U01	37	31,756 (1%)	1,092 (345, 1,311)	236	181,620 (7%)	472 (159, 948)

Definition of abbreviations: P01 = Program Project Grant; P50 = Research Center Grant; R01 = Research Project Grant; R21 = Exploratory/Developmental Research Grant; R44 = Small Business Innovation Research Grant; U01 = Research Project Cooperative Agreement.

All costs are in units of $1,000. All data were obtained from the publicly available National Institutes of Health Research Portfolio Online Reporting Tools (RePORT). Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) are found at http://report.nih.gov/categorical_spending.aspx. Clinical projects are those categorized in RCDC as "Clinical Research" or "Clinical Trials." Total NHLBI extramural funding in fiscal year 2010 was $2,441,772,050. Values for numbers of projects, total funding for each mechanism, and median (25th, 75th percentiles) costs per project were calculated using the SAS version 9.2 "Proc Tabulate" procedure.

those who can at some level understand and translate along the way.

To illustrate the intellectual diversity of the NHLBI's HLB portfolio, we used the NIH funding database publicly available on the NIH RePORT website (25), "*Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC).*" The RCDC system uses sophisticated text data mining (categorizing and clustering using words and multiword phrases) in conjunction with NIH-wide definitions used to assign projects to categories. We extracted and reported here funding data only about those projects that were (*1*) active in fiscal year 2010, (*2*) performed in an extramural location (outside the NIH), and (*3*) were funded or primarily administered by the NHLBI. We designated projects as clinical if they were categorized as "clinical research" or "clinical trials." We report funding levels according to research mechanism (Table 1), to clinical status, and to RCDC categories that include the great majority of HLB research (Tables 2 and 3); it should be noted that the categories are not mutually exclusive. We calculated values for numbers of projects, total funding, and quartile costs per project according to mechanism or topic using the SAS version 9.2 "Proc Tabulate" procedure. The data indicate a generally well-balanced distribution of NHLBI funds among clinical and nonclinical projects across topics and funding mechanisms. The individual research project grant (R01) mechanism predominates funding both for the clinical and nonclinical awards, being by far the most prevalent for the latter, whereas the cooperative agreement (U01) mechanism is used by many more clinical projects. Using another NIH tool that tracks published acknowledgments to NHLBI awards, we estimated that the grant portion of the portfolio illustrated here has generated more than 45,000 publications garnering approximately 2.4 million citations to date. (We are assuming that all NHLBI grantees comply with the obligation in their grant awards to include an acknowledgment of NIH funding in all manuscripts resulting from their NIH-supported research [26].)

TABLE 2. FISCAL YEAR 2010 EXTRAMURAL NHLBI PROJECTS (INCLUDING ALL MECHANISMS) BY RCDC TOPICS THAT TRANSCEND DISEASE CATEGORIES

	Nonclinical Projects			Clinical Projects		
RCDC Topic	No.	Total Funding (% Extramural Funding)	Median Cost per Project (25th, 75th Percentiles)	No.	Total Funding (% Extramural Funding)	Median Cost per Project (25th and 75th Percentiles)
All NHLBI	4,279	1,402,315 (57%)	373 (249, 410)	2,110	1,039,457 (43%)	375 (138, 620)
Aging	194	126,773 (5%)	384 (328, 471)	225	158,832 (7%)	441 (234, 738)
BBSS	27	10,644 (<1%)	347 (137, 394)	91	43,760 (2%)	370 (140, 636)
BSS	62	23,336 (1%)	333 (180, 394)	328	165,222 (7%)	430 (146, 724)
Bioengineering	487	312,832 (13%)	374 (212, 568)	214	128,412 (5%)	393 (197, 661)
Biotechnology	685	344,337 (14%)	379 (249, 449)	229	132,881 (6%)	399 (135, 719)
CER	2	328 (<1%)	164 (—)	88	76,779 (3%)	454 (50, 760)
Gene therapy	83	54,126 (2%)	386 (228, 557)	22	20,779 (1%)	437 (325, 1,868)
Genomics	92	85,165 (3%)	414 (371, 1,598)	134	92,047 (4%)	619 (285, 781)
Nanotechnology	43	83,237 (3%)	393 (212, 707)	6	4,314 (<1%)	350 (133, 1,609)
Pediatrics	263	128,799 (5%)	370 (233, 415)	320	182,147 (7%)	384 (143, 719)
Prevention	292	135,839 (6%)	369 (229, 419)	570	317,302 (13%)	436 (149, 733)
Stem cells	411	190,552 (8%)	378 (233, 415)	140	74,160 (3%)	371 (136, 544)
Trials	—	—	—	444	323,579 (13%)	429 (164, 729)

Definition of abbreviations: BBSS = basic behavioral and social sciences; BSS = behavioral and social sciences; CER = comparative effectiveness research.

All costs are in units of $1,000. All data were obtained from the NIH Research Portfolio Online Reporting Tools (RePORT). Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) are found at http://report.nih.gov/categorical_spending.aspx. RCDC topics are not necessarily exclusive of one another (hence total percentages exceed 100). Clinical projects are those categorized in RCDC as "Clinical Research" or "Clinical Trials." Total NHLBI extramural funding in fiscal year 2010 was $2,441,772,050. Numbers of projects, total funding in each RCDC area, and median (25th, 75th percentiles) costs per project were calculated using the SAS 9.2 "Proc Tabulate" procedure.

TABLE 3. FISCAL YEAR 2010 EXTRAMURAL NHLBI PROJECTS (INCLUDING ALL MECHANISMS) BY RCDC TOPICS THAT RELATE TO SPECIFIC DISEASE CATEGORIES

	Nonclinical Projects			Clinical Projects		
RCDC Topic	No.	Total Funding (% Extramural Funding)	Median Cost per Project (25th, 75th Percentiles)	No.	Total Funding (% Extramural Funding)	Median Cost per Project (25th and 75th Percentiles)
Cardiovascular	1,913	865,499 (35%)	374 (270, 414)	1,005	539,545 (22%)	379 (142, 658)
Atherosclerosis	393	243,991 (10%)	375 (303, 414)	271	160,713 (7%)	401 (198, 722)
CAD	440	221,791 (9%)	380 (323, 420)	267	156,696 (6%)	422 (200, 721)
Heart disease	1,258	595,073 (24%)	375 (286,417)	727	410,409 (17%)	386 (147, 685)
Hypertension	231	105,746 (4%)	370 (312, 401)	111	50,652 (2%)	371 (151, 594)
Lung	697	325,329 (13%)	376 (293, 410)	605	283,649 (12%)	375 (137, 610)
COPD	55	58,142 (2%)	410 (346, 1,730)	84	44,767 (2%)	372 (142, 703)
Asthma	94	40,732 (2%)	373 (249, 400)	144	79,092 (3%)	407 (160, 750)
ARDS	110	61,255 (3%)	384 (335, 410)	82	29,665 (1%)	326 (135, 415)
Cystic fibrosis	42	21,253 (1%)	371 (326, 475)	37	17,928 (1%)	385 (173, 648)
Sleep	55	16,969 (1%)	367 (230, 393)	97	51,527 (2%)	405 (189, 607)
Hematology	406	165,228 (7%)	370 (191, 410)	295	139,989 (6%)	375 (140, 464)
Sickle cell	21	9,325 (<1%)	338 (139, 458)	60	28,774 (1%)	303 (125, 451)
Cooley anemia	9	4,949 (<1%)	394 (373, 429)	9	8,112 (<1%)	411 (390, 1,327)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease.

All costs are in units of $1,000. All data were obtained from the NIH Research Portfolio Online Reporting Tools (RePORT). Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) are found at http://report.nih.gov/categorical_spending.aspx. RCDC topics are not necessarily exclusive of one another (hence total percentages exceed 100). Clinical projects are those categorized in RCDC as "Clinical Research" or "Clinical Trials Total NHLBI extramural funding in fiscal year 2010 was $2,441,772,050. Numbers of projects, total funding in each RCDC area, and median (25th, 75th percentiles) costs per project were calculated using the SAS 9.2 "Proc Tabulate" procedure.

When times are tough, it is tempting to retreat into a conservative, short-sighted investment stance. However, just as with any other long-term investment portfolio expected to weather various conditions, the NHLBI must maintain a strong commitment to investing in a diverse science portfolio that balances risk and long- versus short-time pay-offs. Diversity, like any other investment strategy (5), has downsides, including increased transaction costs, losses of economies of scale, difficult standardization, and internecine conflicts that arise from fundamental preference differences (1) about ultimate goals. Even knowing that we oversee a diverse portfolio still begs a number of other critical issues, such as identifying "hot," potentially transformative, gaps; assessing whether the balances between topics are optimal; considering trade-offs between relatively conservative ("blue chip") and innovative ("high-risk") investments; and applying the concepts of diversity to "big science" infrastructure projects such as NHLBI-funded population cohorts. Nonetheless, in HLB research, the 4 criteria listed by Scott Page (1) for the "Diversity Trumps Ability Theorem" are met: heart, lung, and blood diseases are complex problems; NHLBI funding is highly competitive in all areas, meaning that only high-quality proposals are being funded; the NHLBI funds a widely diverse set of researchers and research groups who are increasingly collaborating with one another; and the research community is large. By recognizing and leveraging each others' strengths and working together (18) to discover, implement, and educate, the diverse HLB research community as a whole will be better poised to continue to improve human health toward achieving the important goals set forward by health initiatives such the "*Healthy People 2020*" (27) and "*The Million Hearts*" (28). A united HLB research community will also be a stronger voice, a voice that can better inform public opinion about the value of publicly funded biomedical science: it takes diversity of vision, teamwork, time, and money to back the best science.

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The Mechanism of the Exercise Hyperpnea

The Ultrasecret Revisited

When Fred Grodins declared the mechanism of the exercise hyperpnea the "ultrasecret" 30 years ago (1), the mystery was already over 90 years old. The central conundrum—how pulmonary ventilation tracks the dramatic increase in metabolic demand that accompanies exercise without apparent change in arterial blood gas composition (specifically Pa_{CO_2} change)—has vexed researchers over the generations. Investigators have generally grouped into two camps. "Humoralists" believe that a blood-borne signal *must* be prominently involved (despite no apparent changes in known chemoreceptor stimuli), citing the close temporal coupling of ventilation to CO_2 output. "Neurogenesists" point to the rapid response of ventilation early in exercise (in advance of the presumed transit time of blood-borne mediators from the exercising muscles to the sites of known chemosensitivity) as evidence that neurally mediated signals from either the exercising muscles (peripheral neurogenic) or radiating from the higher brain centers (central neurogenic) *must* be involved.

The exercise hyperpnea could be argued to be the stimulus for which the ventilatory control system was designed: it is certainly the most common stimulus to ventilation encountered in everyday life. This controversy regarding its genesis is far from settled and is more than of academic interest. Although in healthy subjects ventilatory response to exercise generally does not limit exercise tolerance, the same cannot be said for those with lung disease, particularly those with chronic obstructive pulmonary disease (COPD). Manipulating ventilatory response to exercise, even when we lack certainty regarding the underlying mechanism of the hyperpnea, has proven quite fruitful in improving exercise tolerance in COPD. For example, a quarter century ago we pointed out that, in healthy subjects, exercise training resulted in appreciable lowering of ventilatory response to heavy levels of exercise, apparently because of reduction of the level of lactic acid stimulation of the peripheral chemoreceptors (2). This was only of theoretical interest until it was demonstrated that patients with COPD undergoing exercise training responded similarly and that the postponement of ventilatory limitation (3) (and reduction in dynamic hyperinflation [4]) was associated with substantial improvement in exercise tolerance.

The study of Gagnon and colleagues (5), reported in this issue of the Journal (pp. 606–615), can be considered in this context. Amann and coworkers have reported studies demonstrating that spinal anesthesia, presumably interrupting afferent neural signals from the exercising muscles, yields a reduction in the ventilatory response to exercise in healthy subjects (6, 7). This finding was of academic interest, but of little practical interest, since exercise tolerance was not enhanced. Gagnon and colleagues cleverly realized that patients with COPD might benefit from this strategy. In fact, ventilatory response was appreciably reduced during spinal anesthesia in the patients with COPD they studied. Exercise duration at a constant work rate was thereby prolonged, in close correlation with the delay in ventilatory limitation. Both groups are to be complimented for carrying out a difficult physiologic study and for including a number of cross-checks intended to confirm that interruption of the spinal afferent signals was responsible for the observed effects.

Though the findings are important, questions remain regarding the underlying mechanisms. Do these studies conclusively demonstrate an important role for spinally transmitted signals from the exercising muscles in the hyperpnea of exercise? Weighed against this conclusion are an appreciable body of experimental observations that seem to demonstrate that signals