RESEARCH AGENDA

Opportunities for Research and NIH

The promise of fundamental advances in diagnosis, prevention, and treatment of disease has never been greater.

Francis S. Collins

The mission of the National Institutes of Health (NIH) is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and to reduce the burdens of illness and disability. The power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine. The foundation of success in biomedical research has always been, and no doubt will continue to be, the creative insights of individual investigators. But increasingly those investigators are working in teams, accelerated by interdisciplinary approaches and empowered by open access to tools, databases, and technologies, so a careful balance is needed between investigator-initiated projects and large-scale community resource programs. For both individual and large-scale efforts, it is appropriate to identify areas of particular promise. Here are five such areas that are ripe for major advances that could reap substantial downstream benefits.

CREDITS: (LEFT TO RIGHT) ODOM AND O'HALLORAN/NORTHWESTERN UNIVERSITY; LINDA BARTLETT/NCI, NIH; BILL BRANSON/NCI, NIH; NASA; BILL BRANSON/NIDCR, NIH

High-Throughput Technologies

In the past, most biomedical basic science projects required investigators to limit their scope to a single aspect of cell biology or physiology. The revolution now sweeping the field is the ability to be comprehensive—for example, to define all of the genes of the human or a model organism, all of the human proteins and their structures, all of the common variations in the genome, all of the major pathways for signal transduction in the cell, all of the patterns of gene expression in the brain, all of the steps involved in early development, or all of the components of the immune system. Further development of technologies in areas such as DNA sequencing, imaging, nanotechnology, proteomics, metabolomics, small-molecule screening, and RNA interference are ripe for aggressive investment. Furthermore, these technologies will spur the production of massive and complex data sets and will require major investments in computational biology.

As one example, the Cancer Genome Atlas (*1*) is now poised to derive comprehensive information about the genetic underpinnings of 20 major tumor types. This information will likely force a complete revision of diagnostic categories in cancer and will usher in an era where abnormal pathways in specific tumors will be matched with the known targets of existing therapeutics. Another example is the opportunity to understand how interactions between ourselves and the microbes that live on us and in us (the "microbiome") can influence health and disease (*2*).

Translational Medicine

Critics have complained in the past that NIH is too slow to translate basic discoveries into new diagnostic and treatment advances in the clinic. Some of that criticism may have been deserved, but often the pathway from molecular insight to therapeutic benefit was just not discernible. For many disorders, that is now changing. Three major factors have contributed to this: (i) the discovery of the fundamental basis of hundreds of diseases has advanced dramatically; (ii) with support from the NIH Roadmap, academic investigators supported by NIH now have access to resources to enable them to convert fundamental observations into assays that can be used to screen hundreds of thousands of candidates for drug development; (iii) public-private partnerships are being more widely embraced in the drug-development pipeline to enable biotech and pharmaceutical companies to pick up promising compounds that have been effectively "de-risked" by academic investigators and to bring them to clinical trials and U.S. Food and Drug Administration (FDA) approval.

As one example, the NIH Therapeutics for Rare and Neglected Diseases (TRND) (*3*) program will allow certain promising compounds to be taken through the preclinical phase by NIH, in an open environment where the world's experts on the disease can be involved. Furthermore, as information about common diseases increases, many are being resolved into distinct molecular subsets, and so the TRND model will be even more widely applicable.

The first human protocol (for spinal cord injury) involving human embryonic stem cells (hESCs) was approved by the FDA in 2009, and the opening up of federal support for hESC research will bring many investigators into this field. The capability of transforming human skin fibroblasts and other cells into induced pluripotent stem cells (iPSCs) opens up a powerful strategy for therapeutic replacement of damaged or abnormal tissues without the risk of transplant rejection (*4*–*6*). Although much work remains to be done to investigate possible risks, the iPSC approach stands as one of the most breathtaking advances of the last several years, and every effort should be made to pursue the basic and therapeutic implications with maximum speed.

Benefiting Health Care Reform

U.S. expenditures on health care now represent 17% of our Gross Domestic Product, are continuing to grow, and are excessive as a percentage of per capita gross income com-

National Institutes of Health, Bethesda, MD 20892, USA. E-mail: collinsf@mail.nih.gov

Published by AAAS

pared with other developed countries. Yet few would argue that the quality of care is what it should be. Reinventing health care is thus an urgent national priority, and NIH can make substantial contributions. Among projects that must be pursued are the following.

Comparative effectiveness research. NIH has supported clinical studies for many years that evaluate outcomes of medical treatment options. For example, the Diabetes Prevention Program (*7*) demonstrated substantially better benefits of exercise and life-style changes over medication in preventing the onset of diabetes. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (*8*) compared older, cheaper antipsychotic drugs with newer ones, demonstrating that the older drugs worked just as well and had a better side-effect profile. With support from the American Recovery and Reinvestment Act (ARRA), NIH is investing $400 million in such studies in fiscal year (FY) 2009–FY 2010 and expects to continue high levels of support.

Prevention and personalized medicine. Advances in pinpointing individual genetic and environmental risk factors for disease now make it possible to focus prevention strategies more effectively. For example, research to establish the utility of information about individual genetic risks associated with breast cancer, colon cancer, or prostate cancer may help inform the timing of mammography, colonoscopy, or prostate-specific antigen screening. Also, both retrospective and prospective analyses of how individual information about disease risk actually alters health behaviors and clinical outcomes will be critical.

Health disparities research. The health of racial and ethnic minorities, people living in poverty, and other disadvantaged groups in the United States is substantially worse than the health of the overall population (*9*). Any successful reform of the health-care system will require attention to these groups. Using new and powerful tools to disaggregate environmental and genetic contributions, NIH will seek to pinpoint causes of health disparities and to point the way toward solutions.

Pharmacogenomics. There is compelling evidence of a correlation between genotype and drug response for more than a dozen drugs (*10*), and that number is growing. Prospective studies will be needed for many of these applications, if FDA is to be convinced that genotyping should be required on the label and if insurance companies are to be persuaded to reimburse for the cost of genotyping.

Health research economics. Although the major justification for biomedical research will always be the relief of human suffering and the prolongation of life, further precision is needed in assessing the economic value of research initiatives, especially those that are large and expensive. Models that attempt to capture this cost-benefit balance in Disability Adjusted Life Years (DALYs), Quality Adjusted Life Years (QALYs), Value of Investment approaches, or other metrics are only partially successful in providing the kind of information that policymakers need. NIH plans to initiate a grants program to encourage development and application of more rigorous models.

Focusing More on Global Health

Much of recent global health research has justifiably been focused on AIDS, tuberculosis, and malaria (*11*). It is also critical to go beyond the focus on the "big three" diseases to neglected tropical diseases of low-income countries that contribute to staggering levels of morbidity and mortality. In collaboration with other sources of support such as the Bill and Melinda Gates Foundation, NIH can play a major role in ramping up the discovery of novel targets in both pathogen and host and work to facilitate advances in prevention, diagnostics, and therapeutics. Helping to build capacity and training opportunities in the developing world will be a critical component of such progress. Additional resources will also be needed to respond to the growing challenge of chronic noncommunicable diseases and injuries.

Reinvigorating and Empowering the Biomedical Research Community

The U.S. biomedical research community has been under stress since the flattening of the NIH budget in 2003 and may potentially face even more severe disruptions at the end of ARRA funding in FY 2011. Looking toward the future, a critical feature must be an emphasis on innovation. Although the two-level NIH peer-review process is much admired and much copied around the world, its potential tendency toward conservatism is a chronic concern and invariably worsens when funding is very tight. Recognizing these problems, NIH announced a series of concrete steps in June 2008 to enhance the peer-review process (*12*). Effects of these new steps will be closely monitored, and additional reforms to encourage innovation will be undertaken as needed. Meanwhile, it will be critical to resist political attacks on certain areas of sensitive research (such as drug abuse and sexually transmitted diseases); peer review should remain the appropriate standard for making funding decisions.

The success of biomedical research rests squarely on the robustness of NIH training programs for the next generation of basic and clinical scientists. These training programs face many challenges: (i) the number of supported positions is insufficient to support all of the best applicants; (ii) stipends for graduate students have failed to keep up with inflation; (iii) the relative paucity of new faculty positions over the last few years has forced many talented scientists to remain for long periods in postdoctoral positions; (iv) the typical age at which an investigator obtains his or her first independent NIH grant support has risen to 40 or older; (v) training programs to encourage underrepresented minority participation have thus far generally failed to generate a scientific workforce that resembles the rest of the nation. Solutions in all these areas are badly needed. One initiative that could encourage earlier independence of the most talented young scientists would be a program modeled after the Whitehead Institute Fellows program, where carefully chosen scientists who have just obtained Ph.D., M.D., or M.D.-Ph.D. degrees are provided with laboratory space, technical support, financial resources, and senior mentorship, but are allowed to pursue independent projects, effectively skipping over 5 years or more of postdoctoral training.

Finally, it is time for NIH to develop better models to guide decisions about the optimum size and nature of the U.S. workforce for biomedical research. A related issue that needs attention, though it will be controversial, is whether institutional incentives in the current system that encourage faculty to obtain up to 100% of their salary from grants are the best way to encourage productivity.

Recruiting, retaining, and empowering scientists from many disciplines to work together, supported by a stable trajectory for biomedical research support, are critical to realize the unprecedented opportunities that lie in front of us. It is time to be bold.

References and Notes

1. TCGA, http://cancergenome.nih.gov.
2. Human Microbiome Project, http://nihroadmap.nih.gov/hmp/.
3. TRND, www.rarediseases.info.nih.gov/.
4. K. Takahashi, S. Yamanaka, *Cell* **126**, 663 (2006).
5. K. Takahashi *et al.*, *Cell* **131**, 861 (2007).
6. J. Yu *et al.*, *Science* **318**, 1917 (2007).
7. Diabetes Prevention Program Research Group, *N. Engl. J. Med.* **346**, 393 (2002).
8. J. A. Lieberman *et al.*, *N. Engl. J. Med.* **353**, 1209 (2005).
9. Healthy People, www.healthypeople.gov/.
10. D. A. Flockhart *et al.*, *Clin. Pharmacol. Ther.* **86**, 109 (2009).
11. Committee on the U.S. Commitment to Global Health, Board on Global Health, ***The U.S. Commitment to Global Health: Recommendations for the New Administration*** (National Academies Press, Washington, DC, 2009).
12. Enhancing Peer Review, http://enhancing-peer-review.nih.gov/.

10.1126/science.1185055