



NIH SCIENTIFIC MANAGEMENT REVIEW BOARD



September 14-15, 2010

MEETING - SUMMARY

Board Members Present:

Norman R. Augustine, Chairman
 Jeremy Berg, Ph.D.
 Josie Briggs, M.D.
 William R. Brody, M.D., Ph.D.
 Gail H. Cassell, Ph.D.
 Anthony S. Fauci, M.D.
 The Honorable Daniel S. Goldin
 Richard J. Hodes, M.D.
 Stephen I. Katz, M.D., Ph.D.
 Thomas J. Kelly, M.D., Ph.D.

Deborah E. Powell, M.D.
 Griffin P. Rodgers, M.D., M.A.C.P.
 William L. Roper, M.D., M.P.H.
 Arthur H. Rubenstein, M.B.B.Ch.
 Susan B. Shurin, M.D.
 Lawrence A. Tabak D.D.S., Ph.D.
 Harold E. Varmus, M.D.
 A. Eugene Washington, M.D.
 Huda Y. Zoghbi, M.D.

Ex-Officio Members Present:

Francis S. Collins, M.D., Ph.D.

Designated Federal Official:

Amy P. Patterson, M.D., Executive Secretary

September 14, 2010

Opening Remarks

Mr. Augustine welcomed Scientific Management Review Board (SMRB) members, invited speakers, and guests. After reviewing the meeting agenda, the Board approved the minutes from the July 26, 2010, meeting and was reminded of the NIH Conflict of Interest Policy by Dr. Amy Patterson.

Dr. Collins thanked Board members, especially Drs. Rubenstein and Roper, for their hard work in bringing two sets of recommendations to the full Board for a vote at this meeting. He also emphasized the importance of the new charge issued to the Board, namely, the question of whether there are opportunities to improve the efficiency and the scientific innovative potential for translational research at NIH.

Session I: NIH Intramural Research Program

Presentation of the IRP Working Group Recommendation on the Fiscal Sustainability and Utilization of the NIH Clinical Center

Arthur H. Rubenstein, M.B.B.Ch.

Chair, NIH Intramural Research Program Working Group

Dr. Rubenstein thanked the Intramural Research Program (IRP) Working Group and staff for their hard work and perseverance. He reminded the Board that the initial charge to the IRP Working Group was to examine the NIH intramural research program and determine whether its organization and/or administration warranted change. However, given recent NIH internal assessments indicating an urgent need to address the fiscal

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sustainability of the NIH Clinical Center, the Working Group agreed to focus its initial efforts on conducting an analysis of and providing recommendations regarding the fiscal sustainability and utilization of the NIH Clinical Center. Dr. Rubenstein described the process used by the IRP Working Group to conduct its work, which included hosting a series of meetings, briefings, and consultations with stakeholders, intramural scientists, the extramural community, and the public.

Dr. Rubenstein noted that in its deliberations the IRP Working Group focused on three intersecting themes that the group would address both separately and in the context of one another—the Clinical Center’s vision and role, governance, and budget.

In terms of the Clinical Center’s vision and role, the IRP Working Group determined that the Clinical Center has a number of strengths, including providing intramural scientists with the flexibility to pay full attention to research and nimbly respond to new challenges, full funding for patient care, access to cutting-edge technology, the opportunity to conduct high-risk trials for life-threatening diseases, a critical mass of highly-skilled individuals, the ability to conduct first-in-human studies and rare disease research, support of longitudinal studies, and important training opportunities. Based on this assessment, the IRP Working Group concluded that the Clinical Center is an important national resource and considered whether its resources should be available to external investigators. He added that the IRP Working Group recognized that there are both real and perceived barriers to partnerships between the intramural and external community, as well as intellectual property concerns, that would have to be addressed by the agency if the Clinical Center’s resources were to be more widely available for external investigator use.

In terms of governance challenges, Dr. Rubenstein noted that there is a lack of priority-setting for the overarching clinical research enterprise at NIH. Additionally, there are complexities in the administrative approval process and oversight system which require streamlining in order to maximize use of the Clinical Center.

Regarding budgetary challenges, Dr. Rubenstein reiterated that the current funding for the Clinical Center is unsustainable. This funding source – the “school tax” – relies upon each institute or center with an intramural research program to fund a percentage of the Clinical Center’s budget. As the costs of the Clinical Center escalate, the budget for each institute and center’s intramural program must cover the increasing Clinical Center costs. The Clinical Center has employed cost shifting, which has resulted in unintended and undesirable consequences, including reduced utilization of the Clinical Center by some institutes and centers.

Dr. Rubenstein stated that the IRP Working Group concluded that NIH should: 1) promote the Clinical Center as a national resource rather than just a resource for the NIH intramural program, and 2) prioritize clinical research both within and outside NIH through new governance and budget mechanisms. Any changes in the funding source should ensure fiscal sustainability without having a significant effect on other areas of the NIH intramural community. In keeping with deliberations of the Translational Medicine and Therapeutics (TMAT) Working Group, he stated that the Clinical Center should be an integral part of NIH’s translational efforts.

In response to these conclusions, the IRP Working Group made the following recommendations to the full SMRB for endorsement:

1. The role of the NIH Clinical Center should be to serve as a state-of-the-art national resource, with resources optimally managed to enable both internal and external investigator use;
2. The NIH Clinical Center’s governance should have a simplified structure, capable of developing and overseeing a clear, coherent budgetary and programmatic plan for clinical research; and
3. The NIH Clinical Center budget should be linked to a strong planning process, remain stable in source and equitable in distribution, be effective in attracting and supporting a high quality workforce, and assure efficient use.

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Given the importance of issuing recommendations regarding the fiscal sustainability of the Clinical Center, the IRP Working Group analyzed a spectrum of funding models, assessing the impact of each model on the three intersecting challenges. The IRP Working Group conducted an in-depth analysis of the following five options: the status quo of the current school tax, a modified school tax, a line item in each institute or center mechanism table, a line item in the Office of the Director appropriation, and a direct Congressional appropriation. Based on its analyses, the IRP Working Group recommended that the Clinical Center be funded by a line item in the Office of the Director appropriation, stating that this model maximizes flexibility, while concurrently offering stability and minimizing hierarchical reporting structures. Moreover, this mechanism will balance the priorities of the individual institutes and centers and the agency as a whole, affording the articulation and realization of a trans-agency vision for clinical research.

Discussion

Dr. Varmus asked Dr. Rubenstein to expand upon the IRP Working Group's first recommendation, citing the historical reluctance of the extramural community to use the Clinical Center due to various factors including distance, study control, and costs. Dr. Rubenstein responded that the IRP Working Group recognized that bureaucratic, financial, and intellectual property issues must be addressed in order for the agency to fully embrace this recommendation. However, the IRP Working Group did conduct several extensive stakeholder consultations regarding the use of the Clinical Center by external investigators. He noted that many investigators were unaware of the various Clinical Center resources, particularly related to drug development.

Dr. Fauci clarified that in its proposal, the IRP Working Group is suggesting a one-time budget transfer from the intramural research program to the Office of the Director budget for supporting the Clinical Center. Only when the increase in costs of the Clinical Center in a given year exceeds the overall increase in NIH's budget will funds come out of the entire NIH budget, including a fraction of the extramural research portfolio. He directed the Board's attention to Table 1 in the report for a hypothetical model of these costs. He also emphasized that extramural use of the Clinical Center would have to come at some cost, but how that cost would be assessed would require further analyses.

Dr. Varmus asked whether cost would be a disincentive for extramural scientists. Dr. Fauci speculated that this would not be an issue unless the demands of the study exceeded the capacity of the Clinical Center. Dr. Rubenstein also noted the current underutilization of the beds in the Clinical Center; thus increased occupancy would not necessarily be met with an increase in staffing needs. Dr. Gallin added that only the variable costs for bringing in an additional patient would be charged. The primary resources of the hospital would be available to the extramural community for use. Dr. Katz added that many believe that stringent barriers prohibit the comingling of extramural and intramural funds, which has prevented these types of collaborations in the past. However, given further exploration of legal authorities, this issue may not be a barrier for extramural use.

Dr. Cassell asked if it would be possible for extramural scientists to access the state-of-the-art GMP facility, even if they were not enrolling patients in the Clinical Center. Dr. Gallin answered that, yes, ideally both the GMP facility and other resources could be used if NIH could institute a policy to recover costs from existing grants. Costs could be recovered from new grants if they were included in the original budget proposal.

Dr. Varmus raised several issues related to perceptions about working with the NIH intramural research program, including: investigators losing control when patients are moved into the Clinical Center; institutions being dependent on the Clinical Center; institutions losing credit for the work that is done; and intellectual property issues. He said these perceptual issues must be addressed. Dr. Fauci clarified that the IRP Working Group had considered these issues and concluded that extramural investigators should not be required to collaborate with an intramural scientist, turn over his or her patients, or relinquish ownership of the results.

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Dr. Varmus noted that it will be important to reach out to the extramural community on these issues. Dr. Cassell agreed that this is important, particularly because many in the external community are unaware of the high-quality resources available within the Clinical Center.

Dr. Varmus asked for more discussion of the IRP Working Group's third recommendation regarding the proposed funding source. Dr. Rubenstein noted that there had been lengthy discussion of the five funding options, and the Working Group concluded that the recommended option best supports the Clinical Center while remaining the most feasible. In addition, the fact that the Clinical Center budget would be derived from the overall NIH budget would signal its availability to the extramural community.

Dr. Collins questioned whether the Working Group considered a new charge for the Clinical Center Governing Board of IC Directors, since its establishment would create a new entity. Dr. Katz responded that this group would serve as an advisory committee to the NIH Director and be well situated to understand competing demands on the NIH budget. Dr. Rubenstein added that it will be important for this group to prioritize research projects at the Clinical Center. Dr. Roper noted that it will be important to ensure that use of the Clinical Center would be affordable by the institutes and centers.

Mr. Augustine observed that a potential complication to these recommendations is the ongoing deliberations of the TMAT Working Group, as its considerations of organizational change could affect the Clinical Center and its funding mechanism. Mr. Augustine suggested that the Board endorse the overarching principles of the IRP report and delay a vote on the specific recommendations until the completion of the TMAT report in December. Dr. Katz agreed and noted that Dr. Collins could begin implementing changes in the governance structure of the Clinical Center prior to these deliberations. Dr. Varmus questioned the likelihood of whether the recommendations would need modification following the deliberations of the TMAT Working Group. Mr. Augustine and Dr. Collins clarified that, by approving the recommendations of the IRP Working Group, certain legal requirements of the Board could be triggered that could make it difficult to consider and accommodate the recommendations of the TMAT Working Group. Subsequently, Dr. Rubenstein recommended delaying the vote on the IRP Working Group recommendations until the December meeting, when the TMAT recommendations will be presented to the full SMRB. Dr. Varmus moved to table the vote until December and Dr. Washington seconded the motion. All were in favor of tabling the motion until December.

Session II: Translational Medicine and Therapeutics

Overview of Translational Medicine and Therapeutics (TMAT) Working Group Charge

Arthur H. Rubenstein, M.B.B.Ch.

Chair, Translational Medicine and Therapeutics Working Group

Dr. Rubenstein reviewed the charge to the TMAT Working Group:

- Identify the attributes, activities, and functional capabilities of an effective translational medicine program for advancing therapeutics development; and
- Broadly assess, from a high-level view, the NIH landscape for extant programs, networks, and centers for inclusion in this network and recommend their optimal organization.

Dr. Rubenstein reminded the SMRB that the TMAT Working Group was charged by Dr. Collins to consider how NIH could leverage and organize a wide range of resources and implement the Cures Acceleration Network (CAN) to advance translational medicine at NIH. In addressing its charge, the group is to examine the current NIH infrastructure and initiatives relevant to therapeutics development, keeping in mind the need to synergize and avoid competition with the private sector.

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Current Landscape of Drug Discovery for New Paradigms

Charles M. Baum, M.D., Ph.D.

Senior Vice President for Clinical Programs, Pfizer, Inc.

Dr. Baum, the Senior Vice President for Clinical Programs at Pfizer Inc., discussed several efforts undertaken by Pfizer to address challenges facing drug discovery and development. He noted that despite a substantial increase in spending over the past 20 years to discover new and improved therapeutics, the field has yet to see a corresponding increase in the number of approvals of new molecular entities. The cost of moving a promising compound from the early stages of discovery all the way to the clinic is approximately \$100 million, and much of this cost is for failed projects. Pfizer is attempting to develop a greater understanding of why projects fail in order to minimize late stage failures and associated costs. This will be a key challenge in advancing the field of translational medicine and research.

Dr. Baum stated that in the past, Pfizer had focused on a traditional discovery paradigm—selecting a target or molecule and optimizing the chemistry. This process is now more iterative, with feedback from clinical experience and negative results to inform future studies, especially regarding patient segmentation. Other efforts at Pfizer focus on stem cell biology, general cell biology, and human genetics, which are key components of translational and personalized medicine. These programs focus on molecular profiling, systems biology, and bioimaging, which create a specific profile for the patient to assist in the selection of the correct target. For example, there are extensive efforts in immunology and inflammation which identify subsets of patients with rheumatoid arthritis, lupus, and other autoimmune diseases to gain insights into treating these population subsets more effectively, as well as treating the larger patient population with inflammatory diseases more effectively.

Dr. Baum gave examples of how patient selection informs clinical trials, including lung cancer and crizotinib, which demonstrates a high and durable response rate in a small subset of patients. Patient selection is difficult in most cases, and researchers often lack models and clinically validated biomarkers to study disease effectively. This approach requires that therapeutics developers work with diagnostics companies, health authorities, and regulators. He noted that collaborations, especially with academia, require open innovation networks in which institutions are given access to compound files or antibody libraries. Pfizer is currently implementing these collaborations in limited situations.

Discussion

Dr. Matthew inquired about models for open access in drug development. Dr. Baum responded that discoveries of new targets and unique biology could be shared and that the ability to make small molecules or biologics is where proprietary interests emerge. He noted that sharing increases collaboration, which ultimately benefits the company. Dr. Collins asked if Pfizer would be opening its compound libraries to greater numbers of institutions for high-throughput screening. Dr. Baum responded that Pfizer is open to the possibility, but intellectual property issues must be addressed prospectively. Dr. Washington asked Dr. Baum what the outlook for success might look like under the new paradigm. Dr. Baum said the hope would be to decrease attrition by one third.

Dr. Fauci asked what is done with failed compounds. Dr. Baum replied that there will always be compounds that do not meet the intended endpoint but which might have clinical utility elsewhere. Given appropriate resources, these compounds could be accessed by other investigators. In that same vein, Dr. Cassell noted that the not-for-profit Eli Lilly tuberculosis drug discovery effort gives full access to its entire chemical library. Dr. Varmus asked whether Pfizer would consider the government as a potential partner for discovery. Dr. Baum responded that historically the company has avoided these interactions, with the exception of a partnership for a pre-competitive identification of surrogate markers in the OsteoArthritis Initiative. Currently, however, the company would be open to expanding its collaborations to include partnerships with government.

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Regulatory Perspectives on the Changing Landscape in Therapeutics Development

Jesse L. Goodman, M.D., M.P.H.

**Chief Scientist and Deputy Commissioner for Science and Public Health
U.S. Food and Drug Administration**

Dr. Goodman, Deputy Commissioner for Science and Public Health at the FDA, discussed multiple cultures in the development of therapeutics discovery. Rather than keeping these cultures separate and distinct, they need to be mutually beneficial. Dr. Goodman stated that it is important to have FDA involved in the early phases and throughout the development process. He also acknowledged challenges in information sharing and that knowing when and how to share information (as well as compounds) while protecting intellectual property is a complex problem. The FDA's position is unique, in that it has information regarding both the successes and failures of products, and it can provide guidance without violating intellectual property issues. For FDA to be involved in the early stages of product development, regulatory science capabilities must be enhanced.

The FDA is also cognizant of the need to develop products that offer little to no financial incentives but which represent a public health need. Other concerns include the clinical trials and clinical development process, which should focus on population and disease subsets and should be adaptive and flexible. Data systems are needed to capture data from multiple clinical trials and multiple interventions, and the data should include the natural history of the disease in question (biological and clinical).

Discussion

Dr. Katz asked how FDA is handling patient-reported outcomes. Dr. Goodman responded that patient-reported outcomes are very important, and the agency is working on establishing accurate metrics. He noted that this process is complex because of validation challenges. There must be a greater focus on meaningful benefit, better use of surrogate outcomes, and greater use of accelerated approval mechanisms for serious diseases.

Dr. Cassell inquired how efforts to strengthen the science base at FDA will take advantage of the development of new paradigms within NIH and industry. Dr. Goodman noted that FDA is responsible for overseeing a quarter of the country's economy (food and drugs), and every decision made is a scientific decision, including those pertaining to enforcement. FDA is collaborating with NIH on these issues, and together they have issued a Request for Applications to engage the academic community with an interest in applied regulatory science. Also proposed is a new network of Centers of Excellence in regulatory science, which would build training and capacity in academia.

Panel Discussion

Co-moderators:

- Stephen I. Katz, M.D., Ph.D., SMRB Member
- William R. Brody, M.D., Ph.D., SMRB Member

Panelists:

- Franklin M. Berger, C.F.A., FMB Research
- Ken Duncan, Ph.D., Bill & Melinda Gates Foundation
- Garrett A. FitzGerald, M.D., University of Pennsylvania School of Medicine
- Eric Perakslis, Ph.D., Informaticist and R&D CIO, Johnson & Johnson
- Wendy Selig, M.S., Melanoma Research Alliance
- Mary Woolley, Research!America

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Panelists were asked to share their thoughts on a new paradigm for drug development.

Mr. Berger described his background in underwriting biotechnology companies and business development. He stated that a transformation in drug discovery is already underway in industry, as it is pursuing translational research as more apt business model. He noted that the prospects for greater alliances between NIH, FDA, and industry are promising and exciting.

Dr. Duncan, from the Bill & Melinda Gates Foundation, reported that the Gates Foundation invests in neglected diseases and a small number of therapeutic areas. This portfolio focuses on immediate and urgent issues, such as drug resistance or areas where existing therapies are unsuccessful. The Foundation also focuses on longer-term and more transformational types of medicines, such as the elimination of *P. vivax* and treating acute malarial disease. These foci bring the Foundation into close proximity with NIH and other funding agencies, and subsequently the organization seeks out gaps where its funding can be a catalyst. Dr. Duncan stated that the only way to make real progress in neglected diseases is if all parties work together in a more cohesive and coherent fashion, which will require multidisciplinary teams from early discovery to the clinic. Product development partnerships provide an opportunity to work more closely with NIH. Similar to industry, the Foundation has dealt with significant attrition, that is, candidates failing after a significant investment due to decisions based only on animal data. Dr. Duncan added that the lack of access to available data in the precompetitive space is a source of frustration, as it results in excessive redundancy. The Foundation is working with industry on repurposing compounds for anti-infective purposes and is moving some combination therapies for tuberculosis into Phase 3 clinical trials. While he acknowledged the importance of biomarkers, Dr. Duncan stated that the Gates Foundation cannot invest in them and looks to partnerships with NIH and others in this area.

Dr. Fitzgerald, from the University of Pennsylvania, stated that future models for drug development should focus on a more modular approach. A new model should be more plastic, with the ability to shift teams as necessary to approach particular challenges. NIH's role should be to empower and develop the capability within the academic sector to serve an appropriate role within such a modular approach.

Dr. Perakslis, an informaticist from Johnson & Johnson, described opportunities for more open-source approaches to information, the trend of focusing more on research in pre-competitive areas, and the need for good biomarkers. He urged careful assessment in developing extremely expensive therapeutics that only work for a very small subset of patients, while acknowledging the notion that understanding rare diseases can provide insights into diseases affecting larger populations. He also urged that negative results be published or made available.

Ms. Selig, from the Melanoma Research Alliance, provided the perspective of a nonprofit venture philanthropy organization. She noted that the Melanoma Research Alliance is relatively new and supported by individuals who believe that the current drug development model is ineffective. She stated that the focus of this organization is on translational research without concerns about intellectual property. The Alliance has become the largest private funder of melanoma research in this country and would like to work more effectively with NIH, the National Cancer Institute, FDA, and industry to accelerate progress. One funding strategy is leveraging investments in order to encourage industry to work with academic investigators. An area of focus is combinatorial therapies, which can be complex when more than one company owns the compounds.

Ms. Woolley of Research!America stressed that public and policymaker support is needed to catalyze, implement, and sustain any new paradigm of drug discovery. She noted that this support is essential to securing the appropriate resources and an accommodating environment. She cited public opinion polls indicating that the public wants to be more involved in the process and favors scientists, industry, Congress, funding agencies, and regulatory agencies to work together. She also stated the need for

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regulatory science for faster and more effective therapies. Polls also indicate that the public supports basic research as well as clinical research, and many Americans cite that they have not been engaged in clinical research because they have not been asked. Only six percent of the population has indicated that their medical provider ever talks to them about research of any kind. Moreover, science is too invisible, with only a third of Americans being able to name a living scientist or a scientific institution.

Discussion

Attendees discussed opportunities for NIH to work with industry, particularly in the precompetitive space. Problems include the time to reach approval, FDA's risk aversion, companies going overseas for drug approvals, and the government's conflict of interest policy. Dr. Fauci mentioned the Concept Acceleration Program, which aims to move basic discoveries at NIH through translational research and then link them to companies for development. Dr. Shurin observed that most drug development in cardiology is being done by industry, so the National Heart, Lung, and Blood Institute (NHLBI) focuses on rare diseases or disorders in which there is not a huge profit margin, or a product is no longer on patent. NHLBI is also interested in combination therapies and in working with different companies.

Dr. Perakslis suggested that NIH work as an honest broker for establishing consortia involving multiple companies and academic research centers. NIH also should focus on translation, looking across industry efforts at patient solutions rather than product solutions.

Ms. Selig encouraged NIH and industry to understand and explore the strategies being used in the nonprofit sector, which is creating very innovative research programs.

Dr. Rubenstein questioned whether all of these proposed changes would actually make a difference or whether there is just a cyclic nature to science and drug development that has to run its course.

It was noted that the role of NIH is not to manufacture drugs, but to conduct the science needed to develop drugs. Therefore, it is important to question how NIH should prioritize efforts in the event that it is appropriated \$50 million in CAN funds. NIH already conducts translational research, so the question should be how NIH could use CAN to leverage existing programs and work with industry. Dr. Varmus stated that NCI is already doing plenty of translational work relevant to drug development. Thus, there is some concern about how a more coordinated effort might affect ongoing activities. Dr. Varmus stated that NIH should also consider how it collaborates internally and across institutes and centers, as with the Common Fund and the Clinical Center. Ms. Selig added that CAN funds should be used as a catalyst rather than to create a new program.

Dr. Fitzgerald recommended that NIH focus on developing human capital capable of straddling the translational divide and understanding the drug development process, including the regulatory framework and comparative effectiveness research. Existing programmatic resources in translational research should be aggregated and expanded. The Wellcome Trust funds a translational interdisciplinary research training program that NIH might consider using as a model.

Dr. Duncan urged a more integrated and comprehensive effort in neglected disease, with fewer projects but greater focus. The DARPA-like mechanism, which NIH can use under CAN, could be useful for moving resources around more quickly in response to public health needs and scientific opportunities.

Mr. Augustine observed that the Defense Advanced Research Projects Agency (DARPA) has a very tiny budget compared to the total defense research and development budget, but it has an enormous, disproportionate impact because of features such as investing in high-risk, high-payoff research or

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translation. Another model is Semtech from the semiconductor industry, a model of pre-competitive research in which research was shared to avoid duplication.

Dr. Cassell suggested that NIH become more active in the area of chemical diversity and natural products, which industry has moved away from, but which other countries are actively pursuing. Other areas for NIH investment might include synthetic biology, bioavailability, and new mechanisms for drug delivery.

Dr. Goodman added that the biomedical field needs to develop a model that rewards patient and scientific outcomes in addition to number of publications. Contrary to some perceptions, FDA does not hold back approvals on products that will help a lot of people. It is incremental improvements balanced against risks that require careful consideration and perhaps longer review times.

Dr. Baum suggested that NIH use CAN to focus research on rare diseases and developing biomarkers for patient selection. Pfizer is interested in understanding subsets of patients with common diseases, such as diabetes and hypercholesterolemia, so that targeted treatment regimens can be developed. That research is in the precompetitive area and would benefit greatly from more collaboration with NIH and FDA. NIH also could help with combination therapies by incentivizing companies and academic institutions to work together. Dr. Baum added that the identification of targets and the biology behind those targets is probably still best served within NIH and academic institutions.

Dr. Varmus said that NIH should not confine itself to research on rare diseases, especially in the area of cancer, where the number of targets being identified through genome studies is enormous. This could be an important area for collaboration with industry.

Dr. Tabak reminded participants of the Biomarkers Consortium, which was convened by the Foundation for NIH. Dr. Rubenstein added that an interactive consortium has been created involving several NIH institutes, academia, and industry focused on biomarkers in Alzheimer's disease research.

Public Comments

Steven Rowe from the University of Alabama, Birmingham, commented that one of the failures of large trials on respiratory diseases is that patients are often lumped together. For example, patients with severe bronchitis are grouped with patients presenting with no cough. An improved molecular understanding of those diseases could lend itself well to collaborations, both with small companies and large pharma. NIH resources could be directed toward improving pre-clinical models and those that are predictive of translational results.

Dr. Ray Bergan, Director of Experimental Therapeutics for the Lurie Cancer Center at Northwestern University, said it is important to highlight the fact that we do not know how to move forward in drug development, which leaves a clear path for NIH. The agency might consider setting up incubator projects using CAN funds.

Dr. Robert Califf, Duke University, reiterated the need for individuals trained in different disciplines and the need to recognize that neither industry nor academia knows the best path forward for advancing drug development. He added that there is currently a critical shortage of capacity in informatics and quantitative sciences.

Greg Simon, Pfizer, stated that science is entering a different era, leaving the era of the small molecule blockbuster, which is producing the failures coming out of the pipeline now. Researchers are still operating in a regulatory system that was built in the 1950s, a disease categorization system that was designed in the 18th and 19th centuries, and a communications model that came from the pre-Internet era.

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The implementation of orphan drug policies is not helpful in the new era of genomics and personalized medicine. The challenge is, how does NIH become the host of a virtual enterprise where it uses its resources to administer programs that have begun with the end product in mind? How can NIH create consortia that bring all of the right pieces together, considering its funding models, organizational structure, and conflict-of-interest regulations?

Dr. Goodman suggested that training should involve multiple partners active in product development and evaluation, and include rotations in industry, FDA, and academia. The field also should develop ways for clinical information to feed back into the research system and strategies for bringing informatics and biomedicine together.

Dr. Duncan recommended that NIH sit down with industry and other stakeholders before designing a program to ensure that it is workable for everyone that needs to be involved.

Mr. Berger urged NIH to reach out to biotechnology companies, as they tend to be focused on one or two therapeutic areas.

Dr. Baum encouraged NIH to explore means for sharing and exchanging negative data so everyone can learn and benefit from it.

Bridging the Gap: Defining and Understanding the Necessary NIH Capabilities and Infrastructure

Identifying a Role for NIH: Lessons Learned from Academic Health Centers

Garrett A. FitzGerald, M.D.
Associate Dean Translational Research
University of Pennsylvania School of Medicine

Dr. FitzGerald reiterated his belief that translational science is moving to a more modular approach of drug discovery and development, as compared to the vertically integrated pharmaceutical company. The biotechnology sector has been focused on target identification, proof-of-concept, and drug-ability, whereas the academic effort has focused on target identification and some proof-of-concept in model systems. The modular approach encourages teams to assemble across different sectors and respond to different drug development challenges. NIH should determine how best to empower the academic sector to play a constructive role in this type of interactive modular approach.

A major focus should be in training interdisciplinary scientists in translational medicine and therapeutics. The field of clinical pharmacology used to be well populated, but it has diminished because there is no place to bill for clinical pharmacology as a cost center. The field became unattractive as it came to be viewed as only pharmacokinetic studies, often in Phase 1 and based almost entirely in industry. The disappearance of vibrant pharmacology science has hurt prescribing practices as well as drug development. Some areas of pharmacology have evolved, such as chemical biology and systems pharmacology (i.e., translational pharmacokinetics and pharmacodynamics). But for now, the field is composed of systems biologists (often with a background in engineering or computational science), traditional pharmacokineticists, and modelers. These fields speak different languages, have no integrative glue between them, and have very little understanding of human biology or human pharmacology. Drug companies have tried to integrate the disciplines by superimposing a new structure aimed at crossing silos, and NIH has attempted integration through the CTAs, primarily for T1 translation. The problem is that translation requires several disciplines from basic to clinical science. It is difficult to attract students to translational science, because the field appears invisible and under-resourced.

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Dr. FitzGerald suggested branding the field as “translational medicine and therapeutics,” adopting a unifying nomenclature, and creating a training program in TMAT research. While there are many initiatives at NIH and elsewhere in this area, they are often scattered or loosely affiliated. Options for developing TMAT programs include creating training programs within academic centers or aggregating the clinical and translational science institutes that are in the early stages of proliferation. In academic centers, divisional structures would have to straddle all clinical departments while having secondary appointments in basic science departments, and vice versa. Dr. FitzGerald recommended a master's degree in TMAT as a basic program that provides interdisciplinary exposure before specializing in a particular field. This could be built out of the Clinical and Translational Science Awards (CTSA). NIH could also be a leader and repository for distance learning in translational research. There could be options to rotate through industry, FDA, and the Clinical Center, as well as international opportunities. Programmatic initiatives coupled with training would raise the profile of this type of endeavor. They could incentivize the use of existing core resources within NIH and FDA.

Finally, NIH could take the lead on aligning intellectual property policies with a modular approach, which depends on sharing. FDA could create a safe haven for systems pharmacology, allowing drug companies to explore human biology more broadly without having to report every finding as part of an Investigational New Drug (IND) application.

Mary L. Disis, M.D., F.A.C.P
Co-Chair, T1 Translational Research Strategic Goal Committee
Clinical and Translational Science Awards
University of Washington

Dr. Disis observed that the generation of transformational technology and tools requires innovation, scientific rigor, expertise, a culture change, and the scientific collaboration of diverse disciplines, yet these tools are not being extrapolated into T1 drug development nor are they being developed for T1 translational research. Many diverse technologies and tools needed for T1 research are siloed and held by different stakeholders. Researchers have been doing “one-offs,” developing tools and leaving them to be used by small groups, but not making them available to larger groups. She noted that although high-throughput technologies are available for target identification, they reach a bottleneck when they approach clinical translation. While most critical tools exist, they are not accessible. This could be a potential area for NIH to assist.

Dr. Disis stated that the CTSA programs could use their experiences to inform the process of translation, and used her CTSA as an example of one approach to addressing barriers. The Institutional Review Board (IRB) ethics review process has also been streamlined and another effort has focused on creating a directory of shared technology resources. This is just a small part of a larger technology engine being developed within the CTSA program to link unique technologies at other CTSA institutions on a national level. An area where NIH could help is in cataloguing and making available resources surrounding transgenic mouse models. She stated the need to take translational research into the community, which requires retooling and streamlining old clinical research centers. NIH also could help the public understand the value and meaning of translational research.

The CTSA program has developed many best practices and learned many lessons. NIH should use it as a resource as the agency works to determine its role in translational research. NIH should evaluate the data collected in the CTSA program to assess potential new resources for development and encourage intramural integration around translational science.

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NIH Resources and Programs for a New Paradigm

James H. Doroshow, M.D.
Director, Division of Cancer Treatment and Diagnosis
National Cancer Institute, NIH

Dr. Doroshow described NCI's drug development program, which is 55 years old and has undergone recent changes, including exploring different ways to conduct early drug discovery, changing early-phase clinical therapeutics programs, looking at how to improve delivery of biological agents and small molecules, and conducting clinical trials more effectively. However, NCI did not have adequate medicinal chemistry, high-throughput screening, and chemical biology resources. To address these needs, NCI created the Chemical Biology Consortium, which provides resources for early-phase proof-of-concept, proof-of-mechanism studies; high-throughput screens for medicinal chemistry; and pharmacology and toxicology studies. This program provides support for projects that are difficult to do, are high-risk, and require resources that are not traditionally available to academic investigators.

Susan Old, Ph.D.
Deputy Director
Therapeutics for Rare and Neglected Diseases Program, NIH

Dr. Old presented an overview of the NIH Chemical Genomics Center, a program focused on discovery. She noted that it is part of the Molecular Libraries Program, which is a high-throughput screening program of targets identified elsewhere and involves collaborators from all sectors. This library currently contains approximately one million small molecules. The Center works on assay development, screening informatics, paradigm development in chemistry, and novel toxicology assays that are not model- or cell-based. Personnel are well versed in the drug development process. One goal is to de-risk research so that others will pick it up and marshal it through the "valley of death." Project management is critical.

The Therapeutics for Rare and Neglected Diseases (TRND) Program, located within National Human Genome Research Institute (NHGRI), studies discovery through proof-of-concept in humans (Phase 2). By focusing on the genome and the proteome, which can be more difficult to target and less understood, the program targets prevalent diseases in the undeveloped world and non-prevalent diseases in the developed world. The program primarily conducts probe discovery in cancer and infectious diseases. TRND is not a service center; rather, it focuses on the science of preclinical development and evaluating the current paradigm for drug development. The program issues solicitations for collaborative projects, which undergo external review. Cooperative Research and Development Agreements (CRADAs), and Memorandums of Understanding (MOUs) are used to work with collaborators. Because it is part of the intramural program, government intellectual property policies apply.

Thomas Miller, Ph.D., M.B.A.
Program Director
Office of Translational Research
National Institute of Neurological Disorders and Stroke, NIH

Dr. Miller described the Rapid Access to Intervention Development (RAID) program, which provides critical resources to investigators attempting to advance promising candidate therapeutics along the pre-clinical development pathway when alternative sources of support are unavailable. Successful applicants gain access to government expertise, therapeutics development, and government contract resources to complete specific tasks in the pre-clinical development pipeline. No funds are awarded to applicant organizations. Currently, not-for-profit organizations and small businesses meeting the eligibility criteria for the NIH Small Business Innovation Research (SBIR) program are eligible to apply for support. RAID provides services for a broad set

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of potentially therapeutic agents, including small molecules, gene vectors, and proteins. These services include product development planning, research-grade manufacture, formulation, pharmacokinetic and absorption, distribution, metabolism, and excretion studies, IND-directed toxicology, and manufacture of a good manufacturing practice (GMP) clinical supply. The program is led and managed by a central office in the National Institute on Neurological Diseases and Stroke (NINDS), and the scientific staff currently resides at NCI. A project team with representatives from 13 NIH institutes and centers has been integral to building relationships across NIH. Applications that fall under RAID's scope are reviewed by the Center for Scientific Review (CSR). To date, the program has approved 23 projects, 11 of which have been completed, leading to six INDs, five clinical trials, and three development partnerships. Approved projects span 20 different diseases, and these diseases fall within the program priorities of 11 of the NIH ICs. The number of applications has nearly doubled over the last two years, with 56 applications anticipated for 2010.

Michael G. Kurilla, M.D., Ph.D.

Director

Office of BioDefense Research Affairs

National Institute of Allergy and Infectious Diseases, NIH

The National Institute on Allergy and Infectious Diseases (NIAID) Product Development Program aims to advance infectious disease product development, specifically addressing unmet public health needs throughout the world. Dr. Kurilla defined the translational research stages as follows: early phase involves IND-enabling activities; Phase 2 involves proof-of-concept studies, and late phase involves later stage Phase 2 through licensure, which are largely the domain of commercial development activities and not an area of NIH focus. The program uses a multifaceted approach: directed funding of grants, partnership awards, contracts in the later stages of product development, research services (e.g., screening, repositories, reagents), and clinical trial infrastructure capacity. The partnership program supports a broad swath of the field, including vaccines, adjuvants, therapeutics, diagnostics, and platforms that would support the development of all of those programs. The Concept Acceleration Program is focused on identifying and advancing promising, novel scientific concepts and potential partners from other federal agencies and elsewhere.

John I. Gallin, MD.

Director

NIH Clinical Center

Dr. Gallin described the three GMP facilities at the Clinical Center. One is the upgraded Pharmaceutical Development Section in the Pharmacy Department, which has existed since 1956. This section specializes in product development, analytical and quality control, and pharmacokinetics and formulates tablets, capsules, sterile parenterals, topical products, and placebos. It is responsible for the 1,100 investigational drugs currently under study at the Clinical Center. It also ensures that all raw materials used in finished products are suitable for human use, maintains accountability records for sponsor and FDA review, and assists investigators with IND filing. The Department of Positron Emission Technology (PET program) manufactures GMP quality radiopharmaceuticals for PET scans for patients under IRB-approved protocols. The PET program's resources include three cyclotrons, 10 hot cells for synthesis of radiopharmaceuticals, and a lab for pharmaceutical quality control and dispensing. There are currently three types of scanners: whole-body scanners, PET/Computed Tomography (CT) scanners, and a High Resolution Research Tomography system. The Center is also assisting in the construction of a new PET magnetic resonance imaging (MRI) facility as part of the Traumatic Brain Injury Initiative. The new PET GMP facility will be in the Clinical Center, meet all new FDA guidelines, and double current capacity. The third GMP facility is the Cell Processing Section in the Department of Transfusion Medicine, whose mission is to provide cellular and gene therapy capabilities to investigators. The resources include a Product Development Laboratory, a GMP Lab, and a group that specializes in regulatory affairs. It supports all the hematopoietic stem cell transplant programs at the Clinical Center. In addition, the NIH Bone Marrow Stromal Cell Transplant Center is

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supported through this program. These three GMP facilities support the NIH intramural program but could be expanded to assist outside investigators.

Discussion

Dr. Rubenstein noted that many activities are already underway, yet the number of drugs being discovered is still stagnant. He questioned whether reorganization would enhance this process. Dr. Miller suggested that reasons for this stagnation include the lack of expertise in optimization of small molecules and medicinal chemistry, the lack of large animal model development, and insufficient collaboration. Applied research is interdisciplinary by nature, and translational research is the applied research of human biology. When combining disciplines is necessary, the field must move to a partnership paradigm. Dr. Kurilla added that one reason progress is slow at NIH is that it does not focus on “me-too” drugs. Many of its concepts tend to be high-risk, very novel, innovative, and require some innovative regulatory science. Finally, NIH has not been adept at handing off products for translation that have reached Phase 2 proof-of-concept.

Dr. Kelly asked whether there are mechanisms for coordination among activities. Drs. Doroshow and Old explained that RAID, TRND, and the Molecular Libraries Program regularly interact, and there is a trans-NIH advisory group. Some of these resources are generalizable, while others are disease specific. Dr. Gallin added that the Clinical Center regularly interacts with TRND, the Molecular Libraries Program, and the CTSAAs.

Dr. Berg expressed concern about encouraging individuals to pursue a career path with training that is not well developed. Dr. Washington asked whether a master’s or doctorate level training program would be preferred. Dr. FitzGerald responded that he favors an introductory degree program after which one could specialize in a doctorate program, such as chemical biology or bioinformatics. The introductory program would provide a common foundation across disciplines and would contribute to “branding” the field.

Dr. Cassell asked how NIH could be guided to capitalize on the large investments in drug discovery and drug development in China, especially opportunities for collaboration.

Dr. Roper recommended creating a visual representation of all of the activities underway at NIH. Dr. Rubenstein added that many in the extramural community might be unaware of these activities.

Dr. Brody and Mr. Goldin urged NIH to find a way to address conflict of interest policies, as they create an impediment for NIH working with industry, which is critically needed.

Dr. Collins provided the group with an explanation of how programs are currently integrated. He showed a graphic that maps NIH programs across the development pipeline from target identification to FDA approval. Individual institutes have many ongoing activities, though not all of the institutes have the necessary capacity or resources for translational research, so there is a need for some centralized services. He asked the group whether there is an opportunity to coordinate these efforts more effectively. Dr. Collins also stated that there is an opportunity to do some process engineering of the pipeline. Other opportunities might exist in developing new training programs and shifting some areas of staffing to include more project managers capable of pushing projects forward to success.

Panel Discussion

SMRB members Griffin P. Rodgers, M.D., M.A.C.P. and William L. Roper, M.D., M.P.H., moderated a panel discussion.

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Panelists:

- Raymond C. Bergan, M.D., Northwestern University
- Robert M. Califf, M.D., Duke University Medical Center
- Brian K. Halak, Ph.D., Domain Associates
- Thomas R. Insel, M.D., National Institute of Mental Health
- William Matthew, Ph.D., National Institute for Neurological Disorders and Stroke

Dr. Bergan commented that some of the confusion and misunderstanding about NIH's intramural program and resources is mirrored in the pharmaceutical industry. NIH could address this confusion by increasing awareness and appreciation of its vast resources and by elevating the stature of translational research. NIH also could increase the freedom and resources given to individuals who want to investigate the translational process, as well as provide guidance to the community on what the process is and what it entails.

Dr. Califf noted that there is a critical lack of individuals in the academic sector who understand this area of applied science, which calls for NIH to create and revise training programs. There also should be a culture change that promotes project management, setting goals, sharing failures, and conducting clinical trials more economically and effectively. The workforce needs to grow in the areas of informatics, biostatistics, systems pharmacology, and systems engineering. Dr. Califf added that conflict of interest policies are daunting.

Dr. Halak stated that his venture capital firm invests in early-stage medical technology. However, because of the pressures in this business, he is less able to invest in the earliest-stages of technology, mostly because of the long lead-time for returns. He urged NIH to reward people who work in this area, even as project managers.

Dr. Thomas Insel, NIMH Director, cautioned that NIH should never aim to be a drug company, but it can focus on ways to re-engineer the system, such as how to determine when it is time to pull the trigger on the biology of a new target. The pipeline is not unidirectional, but rather a complicated web of requiring feedback and numerous reentries. One area where NIH might make a contribution to translational medicine is in re-purposing existing compounds. Dr. Insel also urged NIH to look beyond the artificial distinctions and boundaries between the extramural and intramural programs.

Dr. Matthew urged NIH to conduct an inventory of its translational programs across all institutes and centers. This would help leadership find opportunities for collaborations, as well as potential consolidation of efforts.

Discussion

Dr. Varmus observed that translational research is not just about target identification and drug development. Imaging, radiotherapy, diagnostic testing, biological markers for monitoring disease, immune therapy, cell therapies, vaccines, prevention strategies, devices, gene therapy, siRNAs, and delivery mechanisms for drugs should be part of a translational research repertoire. He urged clarification of the conflict of interest policies—what can and cannot be done as scientists, and what can be done as a government official collaborating with industry. Finally, Dr. Varmus asked the group to consider the development of science that is useful globally, not just nationally.

There was general discussion about the NIH contracts process and whether it allows for timely completion of needed projects.

Dr. Hodes asked whether there should be different tracks for basic scientists and those who want to manage science. Dr. Califf responded that it is becoming easier to integrate the two efforts by providing environments in which basic scientists understand when to approach a project manager or applied scientist with questions

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about how to move things forward. Dr. Bergan added that it is all science, just different aspects of it, which is why multiple fields must be involved.

Dr. Fauci cited the H1N1 flu preparedness response as an example in which government, academia, and industry worked together to identify a suitable solution. Responses included building more industry capacity for vaccine manufacturing, utilizing regulatory sensibility and regulatory science, and financing mechanisms that encouraged companies to accept the risk of making products that are necessary but not highly profitable. An outgrowth of the H1N1 response was the Concept Acceleration Program, which aims to ensure that concepts that emerge from basic science are not ignored or discounted.

Dr. Cassell reminded the group that NIH was once more active in the development of appropriate animal models for evaluation of efficacy; there is currently a void in that area. Dr. Zoghbi concurred.

Mr. Augustine stated that he was struck by the fact that industry is decreasing its willingness to invest in basic science, yet academia and NIH are being called upon to conduct the research that will develop new drugs. The reward and incentive structure in the university setting is not aligned for that type of focus.

Dr. Collins observed that the same things were said about the human genome project that are being said about applied/translational research—it is mindless, individuals would not get enough credit, you have to share your data or give it away. Yet the human genome project attracted bright and energetic people. Most scientists would like to make a difference, but sometimes they do not know how to achieve this goal, which is where project managers could help.

Public Comment

James Jorkasky, National Alliance for Eye and Vision Research, commended the National Eye Institute (NEI) for conducting many translational studies of which the rest of NIH should be aware. Because it is a small institute, NEI must find partners in much of its work, both within and outside NIH, with other federal agencies and with industry. Mr. Jorkasky urged the Board to consider translational successes across NIH as it continues its deliberations.

September 15, 2010

Opening Remarks and Agenda Overview

Mr. Augustine welcomed all in attendance to the second day of the sixth full SMRB meeting. He stated that time would be allotted during the afternoon for public comments with a five-minute maximum, and that longer comments are welcome via written submission.

Translational Medicine and Therapeutics

Session III: Cultivating Partnerships—Setting Goals and Defining Success Partnerships in Drug Discovery and Development

Stephen Eck, M.D., Ph.D.

President

Translational Medicine and Pharmacogenomics, Eli Lilly and Co.

Dr. Eck provided an overview of the history of industry-academic collaborations in drug development, including both constraints and opportunities. Although Eli Lilly began as a company that largely sold

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botanicals for medicinal purposes in the early 1900s, it is now a research-based company—a development that was driven by its ability to interact with academic investigators. Dr. Eck stated that because of the Bayh-Dole Act and other changes, pharmaceutical research would be impossible without academic collaboration. Eli Lilly's collaborations are extremely diverse, ranging from those focused on discovering new tuberculosis drugs to small-scale but detailed investigations of the genetics of schizophrenia drug response. Regarding current conflict of interest issues, Dr. Eck commented that it is important to understand the need for a clear separation between research activities and marketing activities and that all financial arrangements must be explicitly transparent and able to stand up to scrutiny.

Dr. Eck highlighted two distinct cultural and resource differences between academia and industry that provide sufficient impetus for collaboration. The first is the increasingly narrow approach taken by industry to drug discovery and development, with a focus on the aspects of clinical pharmacology that are needed to get a drug to market. A lot of interesting pharmacology is not explored, and many talented people will not work for drug companies for a variety of reasons—which alone is a good reason to increase collaboration. Second, drug companies tend to focus on developing a portfolio and driving top-line revenue growth, remaining agnostic regarding how that goal is achieved. The academic investigator has a vested interest in a particular topic and maintains a sustained focus on that topic.

Dr. Eck stated that in recent years, most work focused on the biology of disease and target identification has taken place in academia and not within industry. However, lead generation through Phase 3 is dominated largely by the pharmaceutical industry, which controls the assets and is somewhat secretive and particular about what gets done and when. Changes are needed, because the period from target identification to a new drug launch has shortened considerably, and as the science moves ahead it needs to be incorporated into the drug development program. More disclosure is occurring about clinical trials, and this trend will likely continue. This increased openness will foster more collaboration and increase the use of outside ideas and talent.

Pharmaceutical companies conduct little post-market research and are more involved in finding ways to maximize the value of a drug. Thus, the focus has been on bringing new drugs forward without proportionate contributions to understanding the biology of diseases. There should be a greater willingness to disseminate new discoveries and ideas quickly so they can be incorporated into practice. Dr. Eck noted the importance of exchanging scientific reagents, tools, and technologies and discussed as an example of the development of PET ligands, which have no proprietary interest to Eli Lilly but are used to study receptor occupancy. Such a tool, if made more broadly available, may contribute to the understanding of receptor biology or other areas of neuroscience.

Dr. Eck reviewed five areas in which academic and NIH research can improve efficiency, productivity, and innovation in drug development: 1) identifying targets; 2) understanding patient heterogeneity; 3) developing biomarkers; 4) identifying unique subsets of patients that are responsive to new drugs; and 5) providing tools to help physicians manage complex information.

He emphasized that preclinical areas of collaboration includes target identification and validation, and innovation requires these steps to be at the forefront. In addition, researchers need to understand patient subgroups that will benefit from a particular target. On the clinical research side, there is interest in biomarker research, comparative effectiveness research, and pharmaco-economic research, particularly in determining what constitutes value.

Dr. Eck stated that regulatory science, which has remained relatively unchanged over the last 20 years, needs to be advanced and regulations need to be reformed. Finally, personalized medicine needs to be implemented in a regulated environment by using sound decision-making techniques. The key to creating effective collaborations is transparency; all cards must be placed on the table, face up. Dr. Eck noted that the Genetic

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Association Information Network (GAIN) has contributed to the public good through close collaborations and the absence of proprietary interests.

Discussion

Dr. Kelly wondered what the best and most efficient role for academia and NIH is in drug development. Dr. Eck suggested that there are many examples that demonstrate that the initial process can flourish well in either an NIH laboratory or an academic laboratory. Dr. Cassell agreed that there should be no compartmentalization and that the role academia plays depends on the individuals involved and the skills they offer. All possibilities and combinations of talent should be explored. Dr. Zoghbi noted that repurposing drugs is an efficient way to advance translational research and that there are many new discoveries in academia that could benefit from the use of existing drugs in the pharmaceutical industry. Pharmaceutical companies, however, are often hesitant to share compounds needed in preclinical trials for a variety of reasons. Dr. Eck said a greater diversity of approaches to some of these ideas is needed.

Panel Discussion

Co-moderators:

- Richard J. Hodes, M.D., SMRB Member
- Eugene Washington, M.D., M.Sc., SMRB Member

Panelists:

- Charles Baum, M.D., Ph.D., Pfizer, Inc.
- Ken Duncan, Ph.D., Bill and Melinda Gates Foundation
- Brian Halak, Ph.D., Domain Associates
- Thomas R. Insel, M.D., National Institute of Mental Health
- Jean-Pierre Paccard, Ph.D., Drugs for Neglected Diseases Initiative
- Eric D. Perakslis, Ph.D., Johnson & Johnson

Dr. Hodes provided an overview and three examples of public-private partnerships in the precompetitive space involving NIH. He also described several features that define successful partnerships. The first example highlighted was the OsteoArthritis Initiative, which is looking at imaging techniques to develop ways in which the biomarkers might be used to support ultimate tests of intervention. To avoid giving undue or inappropriate preference to any private sector entity in exchange for financial contribution, these conversations were initiated on the basis that no special advantage would be given to the partners. The results were enormously gratifying and resulted in a study with a budget of \$50 million, nearly \$20 million of which came from the private sector.

A second effort, the Alzheimer's Disease Neuroimaging Initiative, utilized some of the lessons learned in planning the OsteoArthritis Initiative and established a similar partnership, but contacted a much broader share of the private sector. This initiative also included FDA at a very early stage. In its first five years, NIH contributed \$40 million and the private sector contributed nearly \$27 million. Nineteen companies and two nonprofits were involved, including biotechnology, major pharmaceutical, and imaging companies. The project quickly resulted in a number of products. The initiative included more than 60 centers in Canada and the United States, all with different hardware and software platforms, leading to the development of technologies that allowed these platforms to be harmonized and deposited in a single database. Data were made available in real time to the research community, resulting a phospho-tau and an amyloid peptide that show very strong predictive value in tracking the course of early-stage Alzheimer's disease. This effort has spawned some new and parallel enterprises in Europe, Japan, and Australia, and others are being developed

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that will harmonize these techniques and provide great power for quickly identifying the relative usefulness of various biomarkers.

Another style of public-private partnership can be illustrated by the Biomarkers Consortium and GAIN, which provide frameworks for the private sector and NIH to explore together a variety of issues not targeted to a particular area. These efforts will help foster basic research and enhance clinical trials by expanding the precompetitive space or developing products and technologies. Dr. Hodes reviewed some of the challenges involved, such as shortages of funding, determining what exchanges of nonmonetary resources might occur, identifying what the desired products of the partnership might be, and deciding how intellectual property rights will be handled. NIH has generally conducted peer review in an attempt to ensure objectivity and compatibility with the needs of its partners.

Dr. Washington asked the panelists to discuss what they see as the most important attributes of the partnership cultivation process. Dr. Baum responded that it is important for a partnership to be welcomed by both parties and that shared goals and mutual interests are emphasized from the onset. Dr. Duncan noted that the Bill & Melinda Gates Foundation does not have many partnerships directly with industry, but often works through its grantees to examine best practices. It is conceivable that partners can form a relationship with a specific endpoint in mind from the very beginning. Before moving forward, it is important to establish the appropriate oversights and other procedures for deciding the future direction of the partnership. One successful approach involves establishing mini-portfolio agreements that move a number of different targets through the pipeline.

Dr. Halak agreed that it is important to determine goals up front and ensure that all parties are in alignment and on board before beginning a project. This may be easier when considering some of the precompetitive, more discovery-based projects, because they are more congruent with the perspective in academia. Turning a specific scientific discovery or project into a product becomes more challenging, as the academic researcher often is focused on open-ended questions, while private enterprise is looking for a specific answer. He noted that this is an area where NIH should encourage academicians to pursue specific goals.

Dr. Insel noted that NIH has participated in many of these efforts and has had both successes and failures. He added that it might be helpful to talk about what has not worked in the past. The Foundation for NIH (FNIH), through the Biomarkers Consortium, has been one forum for such discussions. The Institute of Medicine has forums for drug discovery, neuroscience, and other areas where there are opportunities for different partners to come together to discuss possibilities. One lesson learned from the Biomarkers Consortium was the importance of having the right people at the table—those with the authority to speak on behalf of the participating party. Another lesson learned within the neuroscience sector is the importance of having multiple pharmaceutical companies involved in exploring and implementing ideas.

Dr. Paccaud stressed the importance of aligning objectives between partners and gaining the support of the senior officials in the private sector. There should also be a focus on building relationships based on good communication and respecting how each partner works. Dr. Perakslis emphasized the importance of optimizing team size and structure and the usefulness of having a framework of governance.

Dr. Hodes noted a need to look at areas where there has been particular difficulty in interactions with NIH so that modifications and improvements can be made. Dr. Eck said that the rules of operation with the federal government, including NIH, are substantially different from those of the private sector. This can include nonstandard reporting requirements, negotiation difficulties, and the complexities of disclosure requirements.

Dr. Baum stated that there is a great need for shared goals that are mutually beneficial. In the past, uncommitted grants of funds have been made to groups without clear goals or expectations, and often this has not worked out for either party. Dr. Insel commented that it is important to be clear that there is no simple

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way to fund an effort that has not been peer reviewed. Another challenge involves broad solicitations—asking the community to send its best ideas—and finding that most applications are for projects that could not be funded through peer review. Dr. Eck added that the expectations around funding need to be reexamined and that, in working with academic partners, all parties need to contribute. In-kind donations, such as datasets from industry can be valuable, but they are not always accompanied by the funds needed to carry out the research.

Dr. Duncan noted that the Gates Foundation has had good interactions with the intramural program through its grantees, but there have been fewer successes utilizing the contracts that support much of the extramural research. Researchers have commented that working through NIH contracts is often cumbersome and slow, and consequently, it is often difficult to get an effort prioritized and get the data back quickly. Dr. Cassell emphasized the role of flexibility in improving the turnaround time of peer review, which could allow work to begin while the investigator goes through the normal channels to apply for a substantial R01 or other funds.

Dr. Zoghbi raised legal and marketing issues and stated that a cultural change at FDA and pharmaceutical companies is needed, because it is much cheaper to repurpose drugs than to start *de novo* for each new medical problem. Dr. Halak observed that if the goal is to get a product to patients, the entire collaborative and regulatory process must be reviewed. Organizations need to work together and avoid operating in silos.

Dr. Washington turned to the next issue—that of discussing the metrics for success and what they should be for NIH and for public-private partnerships with academic or private partners. Dr. Perakslis replied that the most meaningful partnerships include frequent milestones that show incremental value and build momentum, confidence, and good team relationships. He pointed out that many patients are waiting with late-stage diseases, and many of the most interesting efforts are Phase VI or on the late-stage acquisition side.

Dr. Paccaud reported that the Drugs for Neglected Diseases Initiative (DNDi) enters projects at very early stages and tries to be pragmatic. They use clear milestones for all of their development processes and have checkpoints at joint committees to ensure that funds are being used as efficiently as possible. Dr. Halak stated that metrics may differ for each project, but they should be shared and be at frequent intervals; having near-term goals can help the partners gain momentum as the goals are reached. Dr. Duncan commented that it is important for teams to recognize when things are not going well, such as when a milestone is missed, and deal with these issues as quickly and honestly as possible. Dr. Baum stated that internal advocates might be helpful in determining why progress is stalled and in resolving issues. Also, goals need to be measurable and clearly understood. If the budget allows, a project manager should be in place to keep goals and milestones on track. Dr. Eck added that conflict resolution is key to project success and timeliness.

Dr. Washington opened the discussion for questions and asked the panelists to think about the most important message that should be conveyed to the SMRB and colleagues at NIH regarding the acceleration of drug development. Dr. Califf noted the importance of NIH's current role as a communicator and coordinator and stated that NIH needs to play a more effective role in creating a common forum to share progress. Dr. Cassell stated that there could be a role for the Institute of Medicine Drug Forum in filling this void and that the creation of some interactive tools would be helpful. Dr. Hodes noted the strengthening the partnership between FDA and NIH. Dr. Perakslis mentioned the need to consider the phenotype of the kind of person who could run some of these translational projects, both across the institutes and with the private sector—an extrovert with high energy and high emotional intelligence.

Dr. Paccaud reported that DNDi is trying to understand better the assets of the different institutes and how to access these resources, not only in terms of financing but also in terms of competence and networking. Dr. Halak recommended that NIH do its part to increase collaboration. The U.S. Patent and Trademark Office (PTO) should be involved with drug repurposing because of market protection issues for products that have

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dated composition of matter IP. Centers for Medicare & Medicaid Services (CMS) involvement is important, because in order for companies to advance projects, they need to figure out how reimbursement decisions will impact industry decisions. Thus, collaboration is needed between NIH, PTO, CMS, and industry. The culture among many academic researchers also needs to change so there is increased enthusiasm for applying basic science to the development of actual projects. Tools and resources must be offered, and the need for more program managers should be an area of focus. Dr. Duncan stated that from the foundation's perspective, it would be helpful if NIH supported its grantees in developing partnerships to move projects ahead.

Dr. Baum commented that in the precompetitive area, pharmaceutical companies need to collaborate with academia, NIH, and FDA to advance some of the initiatives around biomarkers for use as surrogate endpoints to spur drug development on a conditional approval basis. Another area of specific interest is immunogenicity; there are a number of issues involving immunogenicity that are not understood well, and there is great interest involving predictive immunogenicity and related questions. Efforts in regenerative medicine around stem cells also would be of great interest. Dr. Baum noted that Pfizer is developing an external innovation network, which would be helpful for drug repurposing.

Dr. Eck stated that NIH has an opportunity to be the neutral convener in many of these areas and to smooth the way for individual collaborations through its relationships with the leaders of these companies, whose senior executives may have interests that are not aligned with NIH interests. Using rheumatoid arthritis as an example, he said that it presents an opportunity to bring together a diverse group of scientists to address this disease.

Section IV: Engaging in a Dialogue with the Public

Mr. Augustine introduced the next panel, moderated by himself and Dr. Fauci, who emphasized the importance of engaging in a dialogue with the public and of crystallizing thoughts about the best way to accomplish this. The panel followed a presentation by Jeff Allen, Executive Director of Friends of Cancer Research.

Jeff Allen, M.D.
Executive Director
Friends of Cancer Research

Dr. Allen discussed public expectations regarding the pace of therapeutics development. He stated that approximately 20 percent of new drugs that enter clinical testing actually reach the market. In oncology, this number decreases to eight. He emphasized the need to communicate these challenges when embarking on new models of translational research and educating the public about the importance of this type of research. Dr. Allen posited that now is the time to revise the models focused on directed translation of biological findings to new medicine, but it is equally important to make sure that the public is informed. The public is looking for fundamental changes and wants to understand the work that goes on at research institutions. Defining the problems and the road forward is vitally important to communicate at the outset, and this information needs to be tailored for the diverse audiences wanting to know more about complex topics such as translational research and drug development. He stated that while no one fundamentally opposes the concept of translational research, most do not know what role they can play. Often, government officials cannot provide information directly to Congress without first being asked—a good example of why a mobilized and educated advocacy community is needed.

Dr. Allen noted a clear role for NIH could be to examine both successes and failures to determine why one drug succeeded and another failed. Public interest in understanding the process will be important in gaining steam. In addition, publicizing a directed work plan and communicating incremental goals along the way helps to maintain involvement and garner support.

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The current infrastructure for clinical research has been referred to as out-of-date; fundamental change is needed. In considering a new approach to conducting translational research, having the right expertise in drug development as part of the peer review process from the beginning is critical in determining the right projects for investment. Although the role of NIH and other agencies often is not well understood in the drug development progress, NIH can be a key driver—if not the major convener—of many of the other entities required for success. Dr. Allen noted that he has seen positive steps in NIH and FDA interactions and believes that the agencies will increase channels of communications and coordinate activities to support both agencies' missions of advancing public health.

Dr. Allen noted that the influenza vaccine could be used as an example of a successful translational effort that can be used to both engage and educate the public about the challenges associated with translational medicine. Dr. Allen concluded by noting that conducting this kind of work behind closed doors, without public engagement, endangers the sustainability of translational medicine in the future.

Dr. Fauci agreed with Dr. Allen's statement that public understanding is needed to garner support for the NIH mission and expressed his concerns about public expectations with the introduction of CAN. It is important to explain that NIH funds concepts developed by NIH grantees and asked how communication with stakeholders about the risks and benefits of translational research could be enhanced. Whenever R01 investigators learn of any initiative that is funded by NIH, they become anxious that resources might be diverted away from fundamental, basic, undifferentiated research. Public input is important in establishing tangible goals and setting priorities. This is where increasing the understanding of NIH's role is important, because the public needs to know that cures do not come directly from NIH; they come from NIH contributing to the work of pharmaceutical companies.

Panel Discussion

Co-moderators:

- Norman R. Augustine, SMRB Chair
- Anthony S. Fauci, M.D., SMRB Member

Panelists:

- Margaret A. Anderson, Faster Cures
- Ken Duncan, Ph.D., Bill and Melinda Gates Foundation
- Jean-Pierre Paccaud, Ph.D., Drugs for Neglected Diseases Initiative
- Amy Comstock Rick, J.D., Parkinson's Action Network
- Steven M. Rowe, MD MSPH, Cystic Fibrosis Foundation
- Gregory C. Simon, J.D., Pfizer, Inc.

Dr. Paccaud commented on the dangers of conflating messages and said that NIH is a basic research funding agency that drives development of ideas to products, but development has traditionally been the role of industry. He stated that it may be beneficial to position NIH as the entity addressing and de-risking research on rare diseases, as this research is often not a focus of industry. Dr. Rowe added that there are a number of parallels to what the Cystic Fibrosis Foundation experienced 10 years ago when it transitioned from primarily funding academic institutions and care centers to conducting active venture philanthropy by funding biotechnology companies and pushing their therapeutics development pipeline. If NIH establishes a program that is an active facilitator and partner to pharmaceutical development, frequent communication will be expected by constituents. The new translational effort will require metrics for progress that are easily understandable by all parties. He suggested that NIH's complexity could be harmonized in a simple diagram that could be used as a communication tool to help set expectations.

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Mr. Simon talked about how to move NIH-funded translational research beyond NIH, noting that the same kind of blue ribbon commissions that look at conflicts of interest could examine congruence of interests. He noted that the United States is the only country that divides industry from government and academia in the way that it does. Although individuals have conflicts of interest and there is corruption in academia and in government, it is not necessary to demonize the institutions because of isolated incidences of scientific or political misconduct. The overwhelming majority of people in the industry are passionate about helping people, but they have to do it in a manner that supports their company's success. Mr. Simon added that it is important to talk about the value of innovation in economic terms and to define diseases. However, it will not be helpful for the NIH translational program to define diseases based on what can be analyzed and attacked if FDA keeps regulating drugs based on antiquated disease categories. NIH and FDA need to discuss the future of medicine, and improvements are needed in career development specifically as they relate to options, funding, and opportunities.

Ms. Comstock Rick observed that communication efforts must take into account the different audiences with different needs—patients and the public, researchers, and Congress. NIH has a huge opportunity to educate the public, not just about translational research, but about basic research and the role it plays. CAN also presents an opportunity for promoting a culture of translational research. She also suggested that NIH could begin a journal for translational research that is willing to publish negative results and use NIH's status and funding to promote the culture of translational research. She noted that Congress does not expect NIH to have all the answers, but it does believe that NIH is the right convener to have this difficult conversation about translational research.

Dr. Fauci warned that because the NIH budget is scheduled to be flat for the next few years, if the CAN budget grows, money will come out of the fundamental, basic research efforts; this would cause a serious problem in communicating with an important part of the NIH constituency.

Ms. Anderson said that FasterCures deals with the same sort of issues that NIH does in terms of explaining progress toward cures. Current headlines are focused on what is working or not working in science and on the status of cures, and the public is becoming more sophisticated in its understanding. Another important piece of the current landscape is the aging Baby Boomers—the sandwich generation—that has elderly parents who are living much longer but suffering from diseases that are more chronic. This occurs in the context of safety and risk, which means there is significant discussion about patients being willing to accept more risk while still relying on a regulatory framework that ensures safety.

Ms. Anderson added that NIH needs to be part of the communication process, and more information about how medical research happens and how different sectors collaborate would be useful. The basic research community needs to be part of this discussion. In addition, the effective delivery of information cannot be done only through the use of websites; there are many excellent patient groups, coalitions, and stakeholder bodies that need to be cultivated and viewed as part of the NIH clientele. It is also important to have eloquent spokespersons for science and translation both within and outside NIH. The message needs to leave the confines of the campus and go to all constituent groups, including Congress. The message also needs to describe the translational research portfolio and how basic research fuels the engines of discovery.

Dr. Duncan noted that the Gates Foundation relies on advocacy, but trying to get the message across regarding why investments for new drugs are important is challenging. Grants that encourage high school students to understand global health issues can help make them receptive to the value of science and technology and help them understand why investment is needed in these areas. It may be useful for the R01 community to engage more with the public.

Discussion

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Dr. Cassell stated that there should be a massive communication effort to discuss not just the role of NIH but also the role of academia and industry. FNIH could house this educational effort and should receive the funds necessary to launch such a campaign. Until the message is delivered clearly, it will remain difficult to fund CAN and NIH at a level sufficient to succeed in developing new therapies and other healthcare technologies. Mr. Goldin added that the American public wants to hear from the officials who are in charge of the program. If NIH wants to undertake successfully this translational activity, the leadership of NIH must go to every congressional district at least every other year and meet with people in high schools, colleges, the Chamber of Commerce, advocacy groups, etc. Modern communication demands that the actual officials and not surrogates do this job. NIH leadership must meet with people who have problems and listen, take notes, and answer questions. NIH leadership needs to meet one on one with the members, not the staff, of Congress.

Dr. Zoghbi stated that prevention, which is just as important as developing a treatment in eliminating disease, needs to receive greater attention. When discussing stories of success, such as the discovery of statins and Gleevec, it is important to make sure people know understand that it can take 25 years from the time a basic discovery is made to actual availability of a treatment.

Mr. Augustine stated that another problem is the culture of the research community itself, which is increasingly academic and structured to reward the publication of papers and not products. Until the incentive structure is addressed, it will be difficult to deal with some of these larger issues. In addition, the conflict of interest issue is an enormous that must be handled properly. Because we live in a competitive world with other countries that follow different sets of rules, there could be some middle ground where we can behave appropriately without handicapping ourselves so severely.

Mr. Augustine requested that each panelist share the single most important thing they would do, if appointed as head of NIH, to navigate these issues.

Mr. Simon recommended rotating office assignments every other month to increase awareness among employees about what is happening across NIH and to encourage people to focus on their common mission.

Ms. Comstock Rick said that launching an external communication effort to educate the public about what NIH does and an effort within NIH would help facilitate a serious conversation about NIH's mission. In addition, NIH needs to think of the American people—the taxpayers—as its primary stakeholders.

Dr. Fauci noted that Dr. Collins said at the beginning of his tenure that basic research is NIH's core effort, but there are also programmatic issues that are critical to the NIH mission; the misperception that NIH leadership is wed only to undifferentiated research needs to be corrected.

Dr. Berg commented that the business model for physician scientists at many academic medical centers is not ideal and that it is essentially impossible to try to develop a real translational research career without ending up back on the clinical side. NIH is interested in providing support, but it is difficult to do this without getting the academic medical centers to use a model that will protect those who do this research.

Dr. Allen stated that there should be a tradeoff—new models of thinking can be embraced and silos can be removed, but the external community needs to do the same. Those who work with the cancer community know that this work can be both highly collaborative and highly fragmented. In addition, many problems have not been identified and are not necessarily inherent to NIH. NIH can call on both the external and internal communities to identify those challenges and try to address them.

Ms. Anderson noted that it is important to talk about all of the efforts and the discrete pieces involved in moving a drug to market and to explain the challenges involved. The research community needs to do a better job of explaining that this process cannot be likened to a factory, and there are no easy fixes. NIH should

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have a stronger voice in talking about all of the sectors in medical research and informing the public about NIH and its work. She noted that the FasterCures report *Entrepreneurs for Cures* focuses on the venture philanthropy sector, which receives a lot of media attention, because these organizations promise to collect money, allocate research dollars, and take what works and leave behind what does not work. She also noted that a greater understanding of the value of clinical trials is needed.

Ms. Comstock Rick expressed concern that conflict of interest rules are being used to explain why certain partnerships cannot move forward. NIH should make a positive plan, seek outcomes, find the partners needed, and address associated barriers.

Dr. Rowe commented that when the Cystic Fibrosis Foundation began venture philanthropy, a significant portion of the medical budget went to a single biopharmaceutical entity instead of their R01 community, which resulted in tension. Ten years later, it appears that a lot of good basic science has come out of the original collaboration, and it is evident from publications by basic scientists that many are using the tool compounds that emerged from discovery efforts that were originally funded by the Foundation. The Foundation facilitated this by generating tool compounds that have been publicly available to their scientists and by clearly communicating the promise of others.

Dr. Fauci noted that communication needs to be improved, but this is difficult to do with a flat budget—seven years of a flat budget represents an actual loss of 3 percent per year. Dr. Paccaud added that, because of the flat budget, NIH should ensure that it is concentrating on its major mission. Dr. Fauci stated that significant activity is devoted to increasing public understanding, but it is not always effective. Ms. Anderson commented that the American public understands cost-cutting and that although it is challenging and difficult, NIH must continue to embrace basic research while also looking at its other role (as exemplified by CAN) and communicating about it.

Mr. Goldin acknowledged that on one hand, NIH's core mission is basic research, but on the other hand, a large part of the American public does not even know what NIH is. He wondered whether experts in communication could think this through and make recommendations on how to approach the problem. Ms. Comstock Rick said that it would be useful to increase understanding among the public about the importance of federal funding for NIH. Mr. Simon noted that one strategy is to impart this information as a specific story about how progress is made in medicine.

Session V: Substance Use, Abuse, and Addiction

Mr. Augustine noted that this is an extremely important topic, with two hours set aside for discussion and public comments. Following Dr. Roper's presentation as Chair of the SUAA Working Group, a formal recommendation would be made to Dr. Collins.

Presentation of SUAA Working Group's Recommendations on Optimal Organization of SUAA Research at NIH

William L. Roper, M.D., M.P.H.

Chair, Substance Use, Abuse and Addiction Working Group

Dr. Roper thanked the members of the working group, as well as the staff and others who worked on their behalf. The Working Group's charge was to recommend whether organizational change at NIH could further substance use, abuse, and addiction (SUAA) research to improve the public's health. Over the last 17 months, the working group has held 12 teleconferences and 3 in-person meetings and has heard from a wide array of individuals, including representatives from NIH, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and others groups from across the relevant communities.

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Dr. Roper began by stating the Working Group's findings that emerging scientific research indicates that there are similar reward pathways underlying compulsive behavior, and many substances that pose the potential for abuse may have similar effects on the brain. Common genetic sites are associated with the risk of abuse-related disorders, and addiction is a developmental disease. In addition, many of those who abuse substances suffer from multiple drug dependencies and/or comorbidities. The Working Group asked both NIAAA and NIDA to identify some high-priority areas of research that they believe are not being addressed sufficiently. NIAAA indicated that there is a need for greater understanding of the pharmacokinetic and pharmacodynamic interactions between alcohol and commonly used therapeutics for other conditions; research on the novel metabolites generated as a result of interactions between alcohol and illicit drugs; more information on the mechanisms through which alcohol increases the risks for certain cancers; and greater understanding about how to encourage patients to seek treatment. NIDA noted a lack of pharmaceutical industry interest in developing therapies to treat addiction; insufficient involvement of the medical community in preventing and treating addiction and alcoholism; the availability of treatments that are not being widely used; and challenges involved in the translation of research results.

A broad range of stakeholders provided input regarding the optimal organizational structure for NIDA and NIAAA. Compelling arguments were made, and a wealth of information and evidence on these issues was provided. For the most part, representatives from the drug abuse research and treatment communities presented arguments in favor of a structural reorganization, indicating that there is compelling evidence regarding synergies in the science, that certain patient populations are underserved (particularly patients with multiple substance dependencies), and that there may be impediments to collaboration and integration between the two largely separate scientific communities.

Conversely, most representatives of the alcohol abuse research and treatment communities preferred a nonstructural approach to reorganization that would maintain the current separate institutes. This would involve a "functional" approach to reorganization in which trans-NIH activities would be established for addiction research. Proponents of this approach cited the benefits of having multiple perspectives brought to bear on common scientific questions and warned about the potential for losing certain research foci as a serious risk of structural reorganization. They also noted the positive aspects of the addiction work being conducted at a number of institutes and gave examples of successful collaborations and other trans-NIH initiatives. Proponents of a functional reorganization emphasized the distinction between licit and illicit substances in terms of public health messages and the stigma attached to drugs versus alcohol.

The deliberations were guided by the *SMRB Report on Deliberating Organizational Change and Effectiveness*, in which the SMRB recommended undertaking a three-step process when considering reorganization: assessing the need for change, evaluating the options for change, and implementing and evaluating the change. Five criteria were identified for the first step, assessing the need for change: is there an immediate crisis; are there unaddressed scientific opportunities; have there been changes in the scientific landscape that merit doing something different; are there evolving or emerging public health needs; and is there a need to improve the quality or efficiency of research? Step two, evaluating the options for change, included possibilities ranging from maintaining the status quo to establishing a new institute comprised of relevant research programs from across NIH (not limited to only alcohol and illicit drugs).

The SUAA Working Group unanimously concluded that the status quo is not ideal for fulfilling NIH's mission and optimizing substance use, abuse, and addiction research. Therefore, members agreed that reorganization is needed to optimize the science and the public's health. Based on this initial conclusion, some key features were identified to be necessary for defining and characterizing reorganization. First and foremost, any reorganization must integrate addiction research portfolios across all of NIH, including substances such as tobacco and behaviors such as compulsive gambling. A new organizational entity should promote a unified vision for addiction research, employ an interdisciplinary approach, maintain flexibility to accommodate changes in the scientific landscape, and implement a multidisciplinary approach to training

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new investigators. Success requires commitment by participants at all levels, including the strong leadership of the NIH Director and Directors of the NIH institutes and centers. It also requires contributions from all stakeholders, including internal staff and extramural investigators.

Two primary options for reorganization are described in the report: create a new institute focusing on addiction, or create a trans-NIH initiative on addiction. The SUAA Working Group recommended unanimously that one of these options be adopted, and described the qualities of each.

Creating a new addiction institute would incorporate drug addiction research from NIDA, alcohol research from NIAAA, tobacco research from NCI, and gambling addiction research from NIDA and NIMH. NIH would need to conduct an agency-wide portfolio analysis to determine which addiction-related programs should be included in the new institute and then identify where non-addiction research activities would be moved. For example, alcohol liver disease could be reassigned to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and fetal alcohol spectrum disorders research could be moved to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Funding for each of these portfolios should not be diminished, but merely transferred with the portfolio to the institute in which it would reside. Regarding implementation, the new institute would require the recruitment of a new director and staff should be transferred from NIAAA and NIDA. It was noted that additional staff might be needed to achieve the new mission. A new strategic plan would be necessary, as would a transition committee to oversee the process, conduct the NIH-wide portfolio analysis, develop the organizational structure, establish a timeline, and more.

The second option—a new trans-NIH initiative on addiction—could be modeled after the NIH Blueprint for Neuroscience Research or the new OppNet for Behavioral and Social Science Research. This initiative would need to be larger in scale and investment than either of these two examples and would require stable and dedicated funding source in order to be successful. Several members of the Working Group posited that a majority of each institute's addiction funds would need to be devoted to this project, and the Office of the Director would need to contribute funds as well. The basic organization of this initiative would include a steering committee with the relevant institute and center directors and working groups tasked with carrying out the various related activities.

Proponents of forming a new institute found the scientific evidence and the public health needs sufficiently compelling to undertake this structural reorganization. In their view, the scientific and public health goals cannot be met by creating a trans-NIH initiative. The new institute would enable the effective promotion of some high-priority areas, such as research on polysubstance abuse, understanding adolescent use, or promoting the public health message that alcohol and drugs can have similar effects on the brain and body.

Those who favored the creation of a trans-NIH initiative found the evidence of scientific opportunity and public health needs compelling, but still questioned whether creating a new institute is the best way to proceed. The suggestion was made that a trans-NIH initiative would be just as successful as creating a new institute. There also was some fear that establishing a new institute would create research gaps, in particular in the alcohol portfolio.

Over the course of the deliberations, the costs and benefits of establishing a new institute were discussed and carefully considered, and it was agreed that implementation would be a significant undertaking. It also might cause considerable disruption in the research community, at least in the short term, and there was concern that the benefits of a new addiction institute would be outweighed by the burden of establishing it. The trans-NIH initiative would be inherently interdisciplinary, bringing unique perspectives to the table in a coordinated way.

Discussion

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Dr. Katz inquired about a timeline for evaluating the success of the proposed functional option. Dr. Roper responded that it was discussed at some length and that the option would need to be given at least three years before it could be judged as being successful or not. Criteria for evaluation were discussed, but not characterized in great detail. Dr. Roper noted that the eight SUAA Working Group members usually were split on many issues and that he would not encourage the NIH Director to take on a structural reorganization involving the merger of NIAAA and NIDA, although there is compelling information indicating that it could produce good results. Dr. Varmus voiced his support for creating a new institute and argued that doing so would not overly burden the NIH Director. He noted that the Working Group had already outlined a good plan for implementing the merger.

Dr. Roper noted that much of the angst about the structural option came from the external community and that within NIH it is understood that there would be disruptions and dislocations, but that ultimately, everybody will get on board because the budgets are there. However, he was struck by the deeply held feelings among many in the alcohol community that this would be a tremendous mistake. Dr. Roper expressed support for adopting a functional integration, which would provide the external community with some reassurance during this transition. Later, if the functional approach does not work, then the structural option could be pursued.

Dr. Varmus responded that resistance would always occur because of the anxiety involved when making any change that might affect individuals' access to funds. He stated that the Working Group has done a good job of identifying the sources of those anxieties, and there would probably be some cost-shifting if a new institute were created. NIH is prepared to create a new institute, he said, which appears to be the best option. He questioned the idea of having a functional test to evaluate whether a trans-NIH addiction initiative would be successful. Dr. Kelly observed that the report was extraordinary and made a very compelling case based on the science that the creation of a new institute is likely the best option. He noted that much effort would be involved in implementing either option.

Mr. Augustine asked whether all of the SUAA Working Group members believed that the status quo is unsustainable and wondered if they supported one option because the other simply was not workable or whether it was strictly a matter of believing that one option was better than the other.

Dr. Zoghbi stated that the reasons for supporting merging the two institutes are based on science and public health and are objectively driven. Most of the arguments against the merger rest on two issues: one is that alcohol should not be considered a drug (stigma), even though alcohol is illegal for teenagers and adolescents, and alcohol is a drug. The second significant argument against merger is the fear that because alcohol has so many other effects on health, that focus would be lost if located within a merged institute. Dr. Zoghbi did not find the arguments for the non-merger options to be persuasive. In addition, establishing a successful trans-NIH initiative would involve most of the addiction money in participating institutes, which means a large sum of both institutes' funds. Merging the two institutes would be simpler.

Dr. Hodes stated that he was persuaded by a combination of seeing this as a more rigorously science-based, trans-NIH rearrangement weighed against what appeared to be a more challenging functional solution involving components from so many institutes.

Dr. Washington expressed support for the trans-NIH initiative option, given the resistance that would be caused internally and externally by a merger and the disruption that it might cause. If the science improved in two to three years, then there would be no reason to take on the additional burden of overcoming resistance and disruption. For either option, a metric of success would be needed.

Dr. Rodgers stated that this has been an evolutionary effort and that, if a single institute for addiction research were to be created, it would appear more reasonable to consider all addiction research.

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Dr. Powell observed that addiction research is important, the science of addiction research has progressed, and the spectrum of addiction research should be addressed. She said she did not believe that a functional solution would work.

Dr. Shurin noted that with the difficulties involved in mandating any structural change, decisions should be driven by the scientific considerations. Both institutes have been in place for a significant period and the evolutionary approach makes a lot of sense.

Dr. Varmus commented that it is time to move forward and create the new institute. Mr. Goldin agreed, adding that implementing a functional solution that involves waiting, testing, and further review would be a mistake. The complex issue of addiction cannot be addressed with \$3 billion or \$4 billion a year through good will. Strong leadership is needed to push the right kind of change forward.

Dr. Collins observed that the discussion reflects the challenge of addressing the complexity involved in making this decision. This and the strong feelings in the scientific community are also indicated by the fact that the advisory council of NIDA voted unanimously in favor of the structural option, while the advisory council of NIAAA voted unanimously against it. There is anxiety about what happens to research funding for particular grantees, but this is about trying to support the best science. Consumers also had strong opinions about this, particularly groups such as Mothers Against Drunk Driving that were strongly in favor of special attention focused on alcohol. Dr. Collins said he was glad to see that during the course of the deliberations the structural model was expanded, because the process must be driven by science. This means all addiction research, which clearly touches other areas outside the two institutes, has to be on the table.

Dr. Collins added that the cost to himself and others around him should not be a defining issue. The discussion around the table was helpful, because it provides a fresh look by those who have not been involved in this process for more than a year, and it is exactly what needed to happen. The opinions around the table were strong and well defended. He said he had received all the information and input needed to reach a conclusion and would do so in the near future.

Public Comment

Dr. Mark Goldman, President-elect of the Research Society on Alcoholism (RSA), commented that RSA is not in favor of a structural merger. The issue is broader than addiction, and this should influence the thinking about how the pieces are put together in multiple institutes. He discussed the involvement of developmental processes that have nothing to do with addiction but that do lead to the use of substances. All the institutes that might be players have yet to be named, and it is time for NIH to confront the notion that the burden and cost of the disease worldwide involves behavioral choices that are not yet fully understood.

Mr. Tom Donaldson of the National Organization on Fetal Alcohol Syndrome expressed concern on behalf of the organization's constituents about a potential structural merger. Fetal alcohol spectrum disorders research has had a well-functioning home at NIAAA for many decades; thus, the idea of disbanding NIAAA is causing much concern within the field. He noted that research shows that the notion that drug and alcohol use occur together is common but is not true. Mr. Donaldson predicted that if a separate addiction entity is created, it will affect the work being informed by NIAAA. He stated that the National Organization on Fetal Alcohol Syndrome is pleased with the development of the option for the trans-NIH functional change.

Mr. James Jorkasky of the National Alliance for Eye and Vision Research (NAEVR), which serves as the Friends of the National Eye Institute, emphasized that NAEVR opposes the merger and is concerned that a portion of the research currently being conducted would no longer occur if the two institutes are merged.

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Dr. Stephanie O'Malley of the Research Society on Alcoholism said that the society is in favor of the functional reorganization for scientific reasons and that it is critical to understand that although alcohol use involves more than addiction; there is real value in having an institute that encompasses different aspects of alcohol use and addiction. The functional approach could address research within the alcohol research community on addiction while preserving the expertise and dialogue on the effects of alcohol on multiple organ systems.

Mr. Lyle Dennis, a partner at Cavarocchi Ruscio and Dennis Associates representing the American Association for the Study of Liver Diseases (AASLD), said that AASLD is opposed to merging NIAAA and NIDA and opposes any other action that would undermine the unique portfolio of life-saving liver disease research that currently is supported solely by NIAAA. Members of AASLD believe that any action taken by the SMRB, and ultimately by Dr. Collins, must clearly benefit patients. He commented that having 18 NIH institutes, centers, and offices involved in liver disease research is system strength. In addition, NIAAA is the sole source of extramural NIH funding on alcohol and liver research, and this focus has led to reaching some significant scientific milestones over the years. He commented on the problems AASLD has with simply moving research to NIDDK. First, in light of expected reductions in funding, it would be problematic for the portfolio to be moved without the funds. Second, scientists recognize that a systems biology approach is essential to study alcohol's interconnected effects on the brain and other organs, but an addiction institute would not be involved in that type of research. Therefore, AASLD urges the adoption of a functional approach to addressing concerns about addiction research while leaving the remaining end-organ damage research in its current successful mode. Mr. Dennis added that if a structural merger occurs, it would be impractical to revert to the current system; however, if only certain functions are merged, the quality of that research could be reviewed and a structural merger could be considered at that time, if necessary.

Dr. Mack Mitchell of Johns Hopkins University emphasized how he relies on research sponsored by NIAAA to advise to his patients about alcohol and how it impacts their health. He noted that NIAAA has taken a lead role in looking at alcohol and its properties of addiction and in looking at the entire spectrum of alcohol use and how it affects health and behavior. Dr. Mitchell said that the American public may be disappointed that NIH no longer has an institute devoted to the study of alcohol, and he added that he hoped the committee would vote in favor of a functional merger that would provide a greater emphasis on addiction without losing the benefits of what has been learned about other aspects of alcohol consumption on health and behavior.

Mr. Augustine thanked the members of the public for sharing their views.

SMRB Vote on SUAA Working Group Recommendations and Report

Mr. Augustine welcomed a motion regarding the group's sentiments about whether the current arrangement needs to be changed. Dr. Roper made the motion that change is needed, which was seconded by Mr. Goldin. The motion passed unanimously (with Dr. Tabak abstaining).

Dr. Varmus then moved to recommend the creation of a new institute of addiction—that is, a merged institute described in the report as Option 1. Mr. Goldin seconded the motion. It was agreed that the possibility would remain to use other descriptors as part of the name of the merged institute, such as substance use and/or substance abuse. After voting, Mr. Augustine announced that the motion carried with a vote of 12 to 3 (with Dr. Tabak abstaining). Executive Secretary Patterson noted that this vote constitutes advice to the NIH Director and not a decision. She added that a report would be developed that reflects the process involved, including the discussions held during this meeting.

Ms. Barbara McGarey from the Office of General Counsel stated that the creation of a single merged institute does not require congressional authorization; the authority to do so is at the level of the Secretary of Health and Human Services. There generally is a 180-day period during which Congress could decide to take further

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action before it becomes effective, and nothing prevents Congress from rejecting the action. Congressional appropriations committees and subcommittees will be required to take notice of the action and alter funding in the future.

Dr. Varmus expressed concern about repeated deferral of a decision about the funding of the Clinical Center and attendant issues while awaiting completion of the report on translational science, which is due in December. Chair Augustine responded that he would work to address this issue and that the issue can be discussed in December if action is needed. Dr. Varmus and Dr. Collins affirmed that the report must be completed on time. Dr. Collins stated that if there is an issue about whether the charge is precise enough, the TMAT Working Group may need to be realistic about the level of specificity that can be achieved in the report. However, he expressed optimism that the report will be available on time, based on the track record of this group.

Closing.

Mr. Augustine thanked Drs. Patterson and Collins, NIH staff, other SMRB members and the public for their participation.

Adjournment.

Mr. Augustine adjourned the meeting at 4:24 p.m.

We certify that, to the best of our knowledge, the foregoing meeting summary of the NIH Scientific Management Review Board is accurate and correct.

Norman Augustine
SMRB Chair

Amy Patterson
SMRB Executive Secretary