

**NIH DIRECTOR'S BLUE RIBBON PANEL
ON THE FUTURE OF INTRAMURAL CLINICAL
RESEARCH**

FINAL REPORT

January 2004

**NATIONAL INSTITUTES OF HEALTH
CLINICAL RESEARCH BLUE RIBBON PANEL**

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INTRODUCTION

In August 2003, Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), convened the Blue Ribbon Panel on the Future of Intramural Clinical Research in response to a convergence of several events.¹ First, construction of the new Clinical Research Center (CRC) is nearing completion, providing an ideal opportunity to review and rethink its role, both within the intramural clinical research program (ICRP) and nationally. Second, the newly developed NIH Roadmap focuses on re-engineering the clinical research enterprise, which provides an opportunity to plan strategically for emerging needs in clinical research. Third, approaches to clinical research in academic health centers around the country are changing in response to an evolving scientific agenda, complex regulatory requirements, and a transformed health care system. The role of NIH's ICRP should be reconsidered against the backdrop of this changing landscape. Finally, a congressionally requested report of the Institute of Medicine (IOM), *Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges* (2003), focused on two relevant aspects of NIH's mission—the intramural research program and its clinical research programs. Specifically, the IOM committee that wrote this report recommended that the intramural program “seek to play a unique and distinctive role in the nation's scientific enterprise.” It also recommended greater integration of NIH's intramural and extramural clinical research programs to strengthen both efforts. In addition, the IOM committee called attention to the “fragmented federated structure” of the intramural research program.

Given the widespread interest in and expectations for NIH's clinical research goals, this is an opportune time to assess the prospects and future directions for its intramural clinical research efforts.

Charge to the Panel

In his charge to the Panel, Dr. Zerhouni expressed his desire that it consider the many factors currently influencing clinical research, particularly patient-oriented and translational research, and recommend 1) ways to energize the NIH clinical research enterprise; 2) strategies for integrating clinical research throughout NIH; 3) guiding principles for the ICRP; and 4) measures for assessing the success of ICRP activities. Specifically, Dr. Zerhouni charged the Panel with answering the following questions:

- In what areas not addressed by other NIH-supported research can the ICRP produce paradigm-shifting research?
- Is the current ICRP portfolio appropriate?

¹ The Panel met three times in 2003: August 6, September 15, and October 31. It received briefings from the following individuals: Richard Cannon, Clinical Director, Clinical Center; John Gallin, Director, Clinical Center; Michael Gottesman, Deputy Director for Intramural Research, Office of the Director; R. Edward Howell, VP and CEO, University of Virginia Medical Center; Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases; Raynard Kington, Deputy Director, NIH; Ruth Kirschstein, Senior Advisor to the Director, NIH; Steve Schimpff, CEO, University of Maryland; Alan Spiegel, Director, National Institute of Diabetes and Digestive and Kidney Diseases; Stephen Straus, Director, National Center for Complementary and Alternative Medicine; and Elias Zerhouni, Director, NIH.

- How can the ICRP complement the overall NIH-supported clinical research enterprise?
- How can this be achieved by reassigning existing resources to excellent, distinctive intramural programs in a steady-state environment?
- What measures should be used to evaluate the success of the ICRP?

This is not the first committee to review NIH's clinical research program or its intramural program, but it is the first to focus in a major way on the clinical aspects of the intramural program.

PANEL INSIGHTS AND PERSPECTIVES

Biomedical research has succeeded in converting many diseases that were once considered lethal into more chronic, treatable conditions. However, it has become increasingly clear that a new approach to clinical research is needed if such efforts are to remain successful. As stated in NIH's Roadmap, "Clinical research is the linchpin of the nation's biomedical research enterprise." Yet clinical research remains a challenging endeavor because of its complexity, its high demands on resources and time, and the regulatory environment within which patient-oriented research must operate. Academic institutions have struggled to find the best way to recognize and reward excellence in clinical research in their promotion and tenure systems. Hence, the influx of new talent into this field has been very slow at a time when opportunities to apply science to health are expanding explosively. Indeed, the prevailing view in the biomedical research community is that the complexity of and demands involved in conducting clinical research and the paucity of well-trained clinical investigators are the rate-limiting factors in efforts to maximize the impact of biological discoveries on health. It is thus significant, but hardly surprising, that re-engineering NIH's clinical research expertise was singled out as an area of emphasis in NIH's Roadmap initiative of 2003.

The biomedical research enterprise is in the midst of an extraordinary revolution in the understanding of human disease. With the completion of the human genome sequence, human biology for the first time is emerging as a bounded problem with a finite set of genes and common variants, transcriptional networks, and biochemical pathways. The opportunity to understand the pathogenesis of human disease in spectacular detail is at hand, and this understanding will drive new and innovative approaches to diagnostics and therapeutics in the decades to come. To improve human health, scientific discoveries must be translated into practical applications. As academic institutions strive to maximize their impact, the NIH intramural program, with its unique resources and professional groups, also must refocus and enhance its efforts in clinical research. Part of this process involves determining what compelling role the NIH clinical intramural program can and should play in this revolution.

In recent years the NIH budget has doubled, and although NIH's intramural research budget is approximately 10 percent of the total budget, it represents a sizable investment, at \$2.7 billion annually. Of that amount, roughly \$900 million is spent on clinical research. Thus, the clinical research program is large by any measure. Moreover, a substantial number of major advances in the diagnosis and treatment of human disease have arisen from previous intramural NIH research efforts. The key question that must be asked at this time is, how can the ICRP lead in the coming decades?

The Panel believes that more can be done to direct the course of NIH's ICRP and take advantage of this pivotal moment in the history of biomedical science. With the research tools now available to clinical scientists, a concerted and proactive effort is needed to fit together the pieces of the human biological puzzle if gains are to be made in the prevention and amelioration of human disease.

Decades ago, the NIH ICRP was widely regarded as the most innovative site of clinical investigation worldwide. Strong scientific and social forces drew an extraordinary number of extremely talented investigators to the NIH campus in the 1960s and 1970s. Few other institutions could match the intellectual firepower at NIH, further motivating the most talented investigators to train there. Previous committees have noted that the NIH ICRP is a "victim of its own success," having bred its own competition. With the remarkable rise in the number of extramural biomedical research programs in U.S. medical schools and universities—in large part due to NIH support—the opportunity for finding first-rate training and career opportunities beyond the NIH campus dramatically increased. In addition, the success of NIH in creating a vibrant extramural clinical research program has made it more challenging for the ICRP to remain a distinctive program.

In addition to the rapid growth in the extramural clinical research enterprise, drastic alterations in the U.S. health care system over the last 20 years have changed the referral habits of practicing physicians. One consequence is that a number of previously robust clinical practices at NIH have found it difficult to maintain the clinical volume necessary for strong training and research programs. In this setting, continued reliance on internal recruitment of intramural investigators has been drawing from an increasingly shallow reserve of talent, with the predictable consequence that many intramural clinical programs today appear to be more evolutionary than innovative. As a consequence, a survey of the intramural clinical research portfolio yields a number of individual bright spots, but the overall impact of the portfolio appears to be substantially less than might be anticipated considering the resources that are concentrated in the NIH campus.

Several issues must be considered as part of any effort to re-engineer NIH's ICRP. First, the completion of the CRC represents a major national investment in clinical research. NIH must define a specific vision for the CRC and justify and support its role both within the ICRP and nationally. Second, through the leadership of the CRC and the rest of the intramural clinical research community, NIH must seek a distinctive role for the ICRP in filling research gaps, taking risks, exerting national leadership, and seeking greater standardization in the national clinical research enterprise. Third, for the ICRP to develop an innovative and distinctive research portfolio that complements that of the extramural community, it must have better means of communicating and interacting with that community. Fourth, it is critical that the ICRP develop novel programs that will attract clinical investigators to Bethesda, both as a training ground and as a place to conduct world class research. To achieve these goals, steps must be taken and methods developed to elevate the status of clinical research within the NIH enterprise. This will require, among many things, an efficient and effective governance and advisory structure. The Panel's recommendations are outlined below.

RECOMMENDATIONS

1. **Revise the NIH intramural clinical research oversight structure.**

a. Create a single high-level oversight committee to replace all existing governing bodies that have oversight responsibilities for intramural clinical research.

- i. The new committee should report to the NIH Director.
- ii. The committee should include representatives of Institute/Center (IC) directors, scientific directors, clinical directors, the CRC Director, and outside representatives.
- iii. The committee should be staffed by the Office of the Director.
- iv. The committee should be responsible for governance, strategic planning, priority setting, and budget development. Importantly, this committee would make recommendations about transdisciplinary clinical initiatives and resource allocation.

b. Create an external advisory committee to the NIH Director to periodically and systematically consider the overall quality and vitality of the NIH ICRP.

- i. This committee would function in an analogous fashion to the IC Boards of Scientific Counselors (BSCs), but would evaluate clinical research across the entire NIH, reporting to the NIH Director at least biennially.
- ii. Although the committee would be advisory only, it should be composed of visible and influential leaders.

c. Strengthen the roles of the Office of the Director and IC leadership in clinical research.

- i. Revise the internal structure for coordinating and managing clinical research at NIH, including the creation of a new position of Deputy Director of Clinical Research in the Office of Intramural Research, who also would assume an influential role in the Office of Extramural Research.
- ii. Maintain the role of the CRC Director as an influential senior leader. It is essential that the position of CRC Director remain an attractive and prominent position within NIH. By recommending the creation of a Deputy Director of Clinical Research, it is not the Panel's intent to demote the position of Director of the CRC. The CRC Director should have a seat on the most powerful committees influencing clinical research at NIH, and be primarily responsible for educational programs in clinical research (e.g., the Core Curriculum in Clinical Research). The NIH Director and the proposed Deputy Director of Clinical Research should determine what reporting relationships best balance the need for direct access of the CRC Director to the NIH Director on fiduciary matters (as is the case with all IC directors) with the need for the CRC Director to integrate CRC programs with those of the entire ICRP portfolio.
- iii. Strengthen the role of the IC clinical directors. The Panel respects the need of each IC to craft its own organizational structure. However, the position and role

of the clinical director in each unit was regarded by the Panel as too variable and, in some cases, weak. The clinical directors should be highly placed, with a direct reporting relationship to the institute director.

- 2. Develop new training and career pathways in patient-oriented research.**
 - a. Strengthen career pathways and mentoring in the ICRP for patient-oriented research that culminate in tenure.**
 - i. Individuals in these pathways should be provided with the necessary infrastructure to achieve success as defined by clearly defined benchmarks. Clear distinctions should be made between the clinical service role and that of investigators with independent research resources.
 - b. Establish a premier, highly visible postdoctoral fellowship program in translational research, administered by the CRC Director, for individuals who have finished clinical residency training.**
 - c. Create an advanced research training program for extramural faculty members in academic health centers who wish to take a sabbatical at the CRC as a means of obtaining “on-the-job” experience in clinical research.**
 - d. Foster the recruitment and retention of innovative patient-oriented investigators in the ICRP by assuring salaries and benefits that are competitive with those at academic health centers.**
 - e. Foster an interactive and creative clinical research environment that will attract outstanding postdoctoral fellows. Postdoctoral fellows will want to participate in those programs that are carrying out disease-oriented research or investigating timely clinical problems that cannot be easily studied in the extramural academic health centers.**
- 3. Continue to emphasize the study of rare diseases at the CRC, and promote a strong emphasis on pathophysiology and novel therapeutics in the ICRP.**
 - a. Initiate trans-NIH programs of patient-oriented research that combine the expertise of several ICs.**
 - b. Make the best use of the unique features of NIH’s intramural research program and its ability to undertake bold and innovative research.**
- 4. Create translational, multidisciplinary intramural and extramural partnerships involving the General Clinical Research Centers (GCRCs), the Children’s Clinical Research Centers (CCRCs), NIH-funded extramural networks, the CRC, and the ICRP.**
- 5. Intramural clinical research, including new programs in patient-oriented**

investigation, should be excellent and distinctive, as well as distinguishable from research conducted at academic health centers.

a. This mandate for change should be the responsibility of the NIH Director, IC leaders, the advisory committees, and the BSCs.

6. Regulatory barriers and impediments to clinical research should be reduced. This would include streamlining the regulatory process and providing adequate, effective infrastructure for supporting clinical research.

DISCUSSION OF RECOMMENDATIONS

Need for Streamlined and Comprehensive Governance of the ICRP

The ICRP portfolio consists of a broad spectrum of activities, ranging from physician-scientists conducting basic research in the laboratory, to translational research studies (including preclinical testing), to clinical investigations. Clinical studies are conducted in the CRC and other sites in the Bethesda area and around the country. Numerous institutes are involved in these activities, sometimes collaboratively, but often singly. As a result, a large number of groups participate in one or more activities that are vital to planning and prioritizing the science and finances of the ICRP, including IC directors, scientific directors, clinical directors (or individuals selected to lead the clinical research efforts in the institutes); BSCs; the CRC Research Steering Committee; the Clinical Center Board of Governors; the Medical Executive Committee; various Institutional Review Boards (IRBs); and the Office of the Director. In addition, institutes vary dramatically in their administrative structures related to clinical research, particularly regarding the titles, roles, and reporting responsibilities of those charged with leading the clinical research efforts. No single body has the responsibility for inter-institute strategic planning for clinical research or for meshing the clinical research plans of all the institutes with the CRC's resources (e.g., beds, examination rooms, personnel, support services, budgeted funds). Thus, because of the complexity of the governance structure for clinical research, it is exceedingly difficult to develop new inter-institute clinical initiatives involving the CRC and other components of the ICRP, even when there is general agreement about the scientific opportunities.

The whole of the ICRP has the potential to be greater than the sum of the individual institute-specific clinical research programs, transcending the missions of the disease-specific institutes. The governance structure should promote the clinical research enterprise in realizing its full potential rather than serve as an impediment to innovation.

There is an urgent need for mechanisms for developing an annual inter-institute strategic plan for the ICRP and assessing its progress, for developing broad support for new inter-institute initiatives, and for ensuring that the requirements of the strategic plan are matched to the resources available in the CRC and at other sites where clinical research is conducted.

Strategic planning and oversight for the ICRP should be provided by a committee selected by the Director of NIH and chaired by an individual from the extramural community. This oversight board should replace the existing complex configuration of oversight and advisory boards relevant

to the ICRP. The Director of the CRC should be a member of the oversight board to ensure integration of CRC planning with the entire intramural clinical research enterprise. While the Panel does not wish to prescribe the relationship between the CRC Board of Governors and the proposed oversight committee it highlights that the intent of this recommendation is to provide streamlined oversight of clinical research and not to diminish the role of the Board of Governors. The Panel believes that the NIH Director and his senior management will be in the best position to forge the proper relationship between the Board of Governors and the new oversight committee. This relationship should be evaluated by the NIH Director and senior officials based on existing charters and fiduciary responsibilities. Other subcommittees might include a group focused on extramural-intramural collaborations. The committee should report to the Director of NIH and be staffed by the Office of the Director.

Additional members should be selected to ensure representation by those knowledgeable about the clinical research programs of the individual ICs as well as intramural physicians who are leaders in the conduct of clinical research. External members should be appointed with expertise in clinical research.

This committee should:

- Recommend to the NIH Director strategic direction and program priorities—both short- and long-term—for the ICRP and CRC programs
- Recommend budgetary changes needed to accomplish these priorities
- Prepare written assessments of progress of ICRP programs
- Prepare written assessments of the CRC and its director
- Assess progress in enhancing the ICRP workforce.

In addition to an oversight board, the NIH Director should appoint an external advisory committee to periodically and systematically consider the overall quality and vitality of the NIH ICRP. This committee would review the ICRP retrospectively and provide advice to the NIH Director on areas for improvement, unmet needs, and opportunities for planning and trans-NIH initiatives. It should have strong representation from members of the individual BSCs who are expert in clinical research. The oversight board described above—largely an internal one—would process the work of the external advisory committee in its oversight of the ICRP.

In addition to centralizing and streamlining the oversight and advisory processes for the ICRP, the NIH Director should strengthen the roles of the NIH Office of the Director and IC leadership in clinical research. Specifically, this requires the creation of a new position, Deputy Director of Clinical Research in the Office of Intramural Research, who would also assume a leadership role in the Office of Extramural Research. It is critical that the role of the CRC Director is maintained as that of an outstanding scientific leader in the clinical research community. The Panel recognizes that this proposal creates ambiguities about the reporting lines of the Deputy Director of Clinical Research and the CRC Director, who currently also holds the title of NIH Associate Director for Clinical Research. The NIH Director and the proposed Deputy Director of Clinical Research should determine what reporting relationships best balance the need for direct access of the CRC Director to the NIH Director on fiduciary matters (as is the case with all IC directors) with the need for the CRC Director to integrate CRC programs with those of the entire ICRP portfolio, which will require direct communication between the two clinical research administrative positions.

Finally, each institute should review its clinical research administrative structure to ensure that those directing intramural clinical research have the title, authority, and resources necessary to accomplish the task, including the resources needed to recruit outstanding individuals when appropriate. Such leadership should report directly to the institute director and should be responsible for ensuring that relevant clinical and laboratory-based investigations are appropriately integrated into translational programs. Each institute needs an administrative mechanism under the institute director for assessing and modifying the current clinical research program in order to maximize scientific progress. Individuals in these positions should be empowered to make decisions and should be held accountable for them.

Further, the composition of and charge to the individual BSCs should be reviewed to ensure that each 1) has sufficient expertise to review the clinical research conducted by the institute and 2) gives appropriate weight to the quality and quantity of clinical research conducted by the institute in judging progress made. The membership of each BSC should include a sufficient number of individuals with expertise in clinical research (perhaps one-third of the standing membership), with additional ad hoc reviewers appointed as needed. The BSC should evaluate at least once a year the quality, quantity, balance, and integration of clinical research into the institute's overall intramural research portfolio. In addition, the boards should be charged with reviewing the educational and training programs of the institutes related to clinical research, paying special attention to the percentage of graduates who go on to engage in clinical research activities. The results of these reviews should be communicated to the oversight and advisory committees described above.

Training and Career Development in an Environment Conducive to Clinical Research

NIH must enhance the recruitment, retention, and promotion of clinical investigators at all levels in virtually every institute. Those investigators must be given the resources to develop effective and innovative programs.

The Panel's review of ICRP training programs revealed that there is no clear career pathway culminating in tenure for clinical investigators. That is, although individuals have achieved tenure while doing clinical research, neither the pathway nor the means to traverse it seem to be clearly laid out for junior investigators. In addition, opportunities exist but are not being exploited for intensive and extensive clinical research fellowship programs and training opportunities for more senior investigators. Nonetheless, despite the rapid growth in the size and stature of the extramural clinical research community, the ICRP remains particularly well suited to training the next generation of clinical investigators. The close clinical/laboratory integration not commonly found elsewhere, the ability to admit patients and perform tests without regard to third-party payers, the subsidizing of patient travel, the protection provided to clinician-scientists from the service demands currently experienced in academic health centers, and the stability afforded by the provision of funding and staff for longer observation periods are all advantages that facilitate the conduct of distinctive projects within NIH.

Strengthen and Reward Career Pathways in Patient-Oriented Research

In general, the environment for conducting bench or basic research at NIH is outstanding. Fellows are surrounded by others with similar interests and are mentored by investigators recognized as leaders in their fields. Furthermore, the infrastructure is outstanding, with exceptional resources and

unlimited possibilities for collaboration. The reputation of senior investigators provides a clear advantage for fellows seeking academic positions following training.

This same environment, however, does not exist for those interested in pursuing clinical research. Although NIH and the CRC have made efforts to improve the environment through the provision of training and course work, the fundamental weaknesses associated with the small number of senior investigators committed to clinical research are serious ones. Further, with the exception of only a few of the large institutes, many institutes lack a well-developed infrastructure for supporting clinical research. Weaknesses include lack of assistance with protocol development, lack of biostatistical and trial design expertise, and lack of ancillary support for patient care.

An additional problem in career development for young investigators interested in clinical research relates to the personnel structure at NIH. Although NIH has identified the need for longer periods of training for those involved in clinical research, problems still exist. Fellows training at medical centers other than NIH will often complete a two- or three-year fellowship followed by appointment as junior faculty. Further, they know that if they are successful they may have the opportunity to remain at that institution as their career matures. With rare exception, this is not an option at NIH, and fellows are often unwilling to spend multiple years in a fellowship position knowing that they will still begin their first academic position at a very junior level and often behind those who trained outside NIH. Even though allotment of resources at NIH is typically limited to tenure-track investigators, there should be a mechanism by which these clinical investigators can receive startup packages.

Further problems exist in allowing fellows to continue for multiple years, as the number of positions available within each research group at NIH is limited (and they are expected to become more limited). Because programs conducting clinical research depend on clinical fellows for clinical support, there is a need to recruit new fellows periodically. Many groups have used the staff clinician appointment as a way around this problem.

Currently, the role of a staff clinician varies widely, from an individual doing service work to a young clinical investigator conducting research. Thus, the recruitment, role, and review of staff clinicians should be redefined. Staff clinicians whose major focus is clinical research should be treated like other tenure-track scientists, recruited through an open search, and provided with independent research resources. They should undergo a tenure process appropriate for clinical research and should be reviewed by the relevant BSC. Perhaps a separate designation, such as clinical investigator, would be appropriate for these individuals. The nontenured staff clinician designation should be reserved for those who truly function primarily in a service role.

Once a clear career path has been established, it is important to ensure that recruitment packages offer sufficient space laboratory and office space and financial resources to be eminently attractive and to provide the tools needed for career and project success. Each institute should develop five-year targets for the net number of tenure-track and tenured investigators (those recruited minus those who leave the institute) for the institute's clinical research program. Each institute's clinical director should be highly involved in reaching those targets—and for the quality of the clinical investigators recruited. The clinical directors will need to receive adequate resources in order to accomplish these goals.

Compensation packages should be improved for young, newly recruited clinical investigators and for senior management. Laboratory and office space in the new Hatfield Clinical Research Center and adjacent buildings should be reserved for investigators who are conducting patient-oriented research, and space must be made available for clinicians with growing programs.

Finally, the organizational structure of the institute intramural programs should more accurately reflect the translational nature, as well as the importance, of clinical research. The structure currently found in many institutes, in which staff clinicians work for a clinical director who in turn answers to the scientific director, has led some to believe that clinical research is separable and less valued than the remainder of the intramural research portfolio. Each institute should explore initiatives and administrative structures to assure the optimum allocation of resources and the most effective program development and evaluation processes. For example, the National Heart, Lung, and Blood Institute assembles clinical and basic investigators with common interests in a separate division with a director who reports directly to the institute director. Although this approach may not be appropriate for each institute, it does provide a good model for developing administrative and institutional structures.

The most fundamental aspect of invigorating the ICRP is the need to attract and retain clinical investigators committed to conducting patient-oriented research. Creating a clear and rewarding career path for such individuals is an essential first step. Without this step, the ICRP will not be able to attract leaders in patient-oriented research who can serve as mentors to those in training and as advisors to those making resource and policy decisions.

Postdoctoral Fellowships in Translational Research

The CRC should develop a centralized clinical research curriculum and training program for individuals interested in translational and patient-oriented research who have completed their clinical residency training. A two- to five-year training program would ensure the production of rigorously trained and committed clinical investigators. This clinical research fellowship would combine didactic training in disciplines such as trial design, biostatistics, and ethics with a research project in one of a variety of areas, including molecular pathophysiology, therapeutic intervention, or outcomes research. The trans-institute faculty would include premier clinical researchers, and eventually this program could define a new accredited subspecialty. A first step might be to create a program that builds on specialty training and leads to a certificate of added competence that might be recognized by accrediting boards. Every institute active in the ICRP should participate by agreeing to mentor trainees accepted into the program once an individual chooses a research program.

Sabbatical Program for Exchange of Faculty Between the Extramural and Intramural Programs

NIH should develop a sabbatical program that will allow more extramural faculty from academic medical centers and industry to spend time in the ICRP and that will enable intramural investigators to spend time in the extramural and private sector research communities. A clinical investigator training program would attract clinical investigators interested in taking sabbatical breaks to teach and would provide access to areas of research unavailable at investigators' home institutions as well as work at other research institutions on multicenter trials.

More specifically, NIH could consider a program for GCRC investigators in patient-oriented research to provide them with a common understanding of the standards and mechanics of patient-oriented research and showcase NIH resources in education and patient care. A program at NIH could be based on a defined curriculum, could be offered by the CRC, and could provide an opportunity for an apprenticeship at the CRC.

Intramural-Extramural Collaborations

In general, the clinical research and training activities of NIH's intramural and extramural programs remain separate and distinct, although the Panel was informed of some cases where collaboration has occurred or is ongoing. Several natural and potentially critical linkages could be made between the two programs to make the best use of the resources and expertise of each.

GCRC and CCRC Multicenter Networks for Translational Research

One of the NIH Roadmap goals is to create centers for translational research. Linking the GCRCs—funded through the extramural program—with the ICRP/CRC for the purpose of conducting translational research could be critical to studies of rare diseases (e.g., metabolic disorders) and to studies of high-profile diseases lacking diagnostic criteria or treatment (e.g., chronic fatigue syndrome, obesity).

Benefits would accrue to both the ICRP and the GCRCs: 1) collaboration would create a critical mass of recruiting centers to increase patient volume/recruitment for studies of importance to both programs; 2) patients could be treated under common protocols at a local GCRC or the CRC; and 3) a partnership between the ICRP and academic centers will enhance the public's awareness of NIH's clinical research program and elevate the regional reputations of the GCRCs.

A similar network could be formed between the CCRCs and the CRC, but with a different rationale. The CCRCs are considerably fewer in number and are often subsumed by GCRCs. Although there are some commonalities in the diseases studied (e.g., obesity, type 2 diabetes), most of the research questions will be different. In addition, the CCRCs already have substantial experience with collaborative, multicenter trials (e.g., Children's Oncology Group, Neonatal Network), but would further benefit from an established relationship with the CRC. Linking the CCRCs with NIH-funded networks and the ICRP/CRC for joint research topics and protocols could facilitate clinical and translational research by providing a forum for centralized review and data management as well as the core facilities that are often lacking in many freestanding children's hospitals.

Improved infrastructure is needed to revitalize the role of GCRCs and CCRCs in translational research and establish them as centers of innovation. A collaboration with the CRC could involve an annual meeting of directors, the participation of CRC leadership in NIH task forces and clinical research advisory functions, the creation of a central clearinghouse for protocol development and regulatory approvals, the provision of centralized data management and statistical expertise, the designation of co-Principal Investigators from the NIH ICRP and one GCRC director, access to specialized testing components available at NIH or individual institutions (e.g., SNPs), and the use of modular budgets. NIH should consider creating incentives for participation by, for example, doubling the reimbursement rate for patients recruited for collaborative studies of high priority for the partnership.

Focus of the ICRP Portfolio

It is axiomatic that the ICRP should continue to invest in the most talented scientists conducting the highest caliber research. The typical model of investigation—research conducted by single investigators or small groups of investigators—will undoubtedly continue and will be successful only if clinical investigation is considered a crucial aspect of the overall NIH intramural portfolio.

Although the ICRP as it is currently configured can continue to support excellent research, the Panel still questioned whether the general research portfolio is sufficiently distinctive from what is found in the extramural community. Future directions should include a focus on research that defines a more distinctive niche in the U.S. biomedical research portfolio and that takes on projects that cannot be as easily conducted in the extramural program. The intramural program is particularly well equipped for the conduct of bold, innovative research and has fewer short-term constraints than the extramural program.

The NIH campus provides extraordinary breadth and depth of expertise in virtually every major discipline of biomedical research. This strength, which is rarely matched in the extramural community, can serve as a powerful catalyst for interdisciplinary work that has the capacity to dramatically advance a field. Indeed, many of the most distinctive advances from the intramural program have come from just this type of interdisciplinary work. In addition, it is increasingly apparent that the pathogenesis of many of the common, major public health problems in the United States cuts across the traditional bounds of NIH institutes and that the overall thrust of the intramural clinical program would be well served by greater inter-institute collaboration and cooperation on projects that relate to clinical and translational investigation.

NIH could embark on a number of trans[institute, interdisciplinary initiatives of considerable scope, each with the goal of defining a significant body of knowledge relevant to the pathogenesis, diagnosis, and/or treatment of major public health problems. The advantages of such an initiative would include the potential for making important advances that will be broadly relevant to public health, facilitated by bringing critical mass to bear on important clinical problems; the potential for engaging the strong basic science of the intramural program in translational research; the ability to galvanize the clinical research community for major initiatives in important disease areas; and the ability of such programs to attract significant new talent to the NIH campus at both the faculty and fellow levels. The Bench-to-Bedside Awards program serves as a superb example of a highly successful program that fosters collaborations among intramural scientists and clinicians in areas of research that have the potential for improving understanding of an important disease process or for leading to a new therapeutic intervention. NIH should continue to foster and even expand this program.

However, despite the notable success of the Bench-to-Bedside Awards, a number of barriers remain to initiating such trans-institute, interdisciplinary efforts. One is inertia. Establishing such programs requires a large amount of work by NIH leadership, a group that is doubtless already over committed. It is challenging to assemble the appropriate individuals, devise a coherent strategy, obtain the needed resources, and maintain programmatic coherence. A second barrier is internal resistance; in an era of flat or modest budget increases, any new initiative will come at the expense of others. Against this backdrop, inter-institute collaboration requires particular nurturing and incentives. In addition, NIH needs to continue to conduct rigorous external review of its

clinical as well as basic science in order to ensure that resources are well aligned with opportunity and productivity.

The success of such efforts depends on a number of factors. First, there is the downside risk that the problems selected may not prove to be ripe for investigation. This risk seems small, given the substantial technologies in genetics, genomics, proteomics, and imaging that have recently been implemented and that can be marshaled within the broad intramural community. In fact, it is unlikely that there has ever been a time when one could more confidently predict that the development of a sound interdisciplinary program would yield important new understandings of human disease. Nonetheless, some matching of these initiatives to the public health impact of the disease and the degree of unmet medical need is likely to maximize the impact of the program. For example, an NIH-wide initiative to understand the pathogenesis of obesity or schizophrenia would have the potential to generate a great deal of interest across the campus and address important clinical areas that are poorly understood. Second, this approach to science, driven from the top down, could carry the risk of producing mediocre science and squelching innovation on the part of the individual investigator. The success of such projects consequently depends on open-minded leadership providing a strong scientific vision and coherent program planning.

In addition to pursuing the pathogenesis of common disease, clinical investigation at NIH could play an important role in furthering the understanding of selected rare diseases. As disease pathogenesis becomes better understood, potential rational targets for therapeutic intervention will become apparent for some of the rare diseases. It is uncommon, however, for these targets to be pursued by the pharmaceutical or biotechnology industries, because the perceived size of the market is too small to justify the expense of drug development. As a consequence, patients with rare diseases and their families commonly do not benefit from advances in research. Nonetheless, it seems possible, if not likely, that a drug targeting a highly validated target (e.g., one for which a causal relationship to disease is firmly established) should on average be less expensive than others, because the risk of lack of drug efficacy, a significant mode of failure in the pharmaceutical industry, is vastly diminished.

NIH could champion the development of new therapies for several of these diseases, as success with such agents would serve an unmet medical need and would have the potential to impact the economics of drug development. However, a number of important questions about such an effort would need to be considered, e.g., questions regarding relationships with private companies for screening of chemical libraries and about how far to take development in-house. Nonetheless, by focusing on diseases in which NIH investigators have special expertise, downstream clinical investigation within the intramural program could be enhanced.

Standardization, Regulatory Reform, and Streamlining

It became apparent to the Panel that the regulatory and review processes for intramural clinical research need to be made more efficient and uniform across institutes in order to encourage investigators to initiate new protocols and to harmonize the demands placed upon clinical research from different regulatory agencies.

In particular, the proposed oversight committee, in consultation with the Human Subjects Research Advisory Committee, should consider mechanisms to make the regulatory process for intramural clinical research more efficient while still ensuring adequate protection for human subjects in

research. In addition, the proposed oversight committee should a) identify procedures that will streamline the protocol approval process; b) encourage the exchange of best practices across ICs in order to establish uniformity; and c) develop educational, consultative, and electronic resources that will assist investigators in the protocol writing and approval process. The committee should prepare a formal report on its findings including recommendations for the Deputy Director of Intramural Research. If he approves the report, he should develop a plan for its distribution and for implementation of the findings.

SUMMING UP

A striking aspect of the NIH campus is the extraordinary breadth and depth of expertise that can be found in virtually every major discipline of biomedical research. This strength can serve as a powerful catalyst for interdisciplinary work that has the capacity to dramatically advance a field. Indeed, many of the most distinctive advances from the intramural program have come from just this type of interdisciplinary work. In this setting, the overall thrust of the intramural clinical program would be well served by greater inter-institute collaboration and cooperation on projects that relate to clinical and translational investigation. The completion of the Hatfield Clinical Research Center represents a major national investment in clinical research and provides a unique opportunity to advance clinical research. Through the leadership of the CRC and the rest of the intramural clinical research community, NIH must aggressively seek a distinctive role for the ICRP in filling research gaps, taking risks, exerting national leadership, and developing an innovative and distinctive research portfolio that complements that of the extramural community. It is critical that the ICRP develop novel programs that will attract clinical investigators to Bethesda, both as a training ground and as a place to conduct world class research.

The Panel developed several recommendations regarding the ICRP's governance and oversight, research portfolio, interactions with the extramural research program, and career development opportunities. While it is the Panel's hope that these recommendations will be useful, they will achieve their intended effect only if each unit within NIH places a high premium on the value of clinical research.