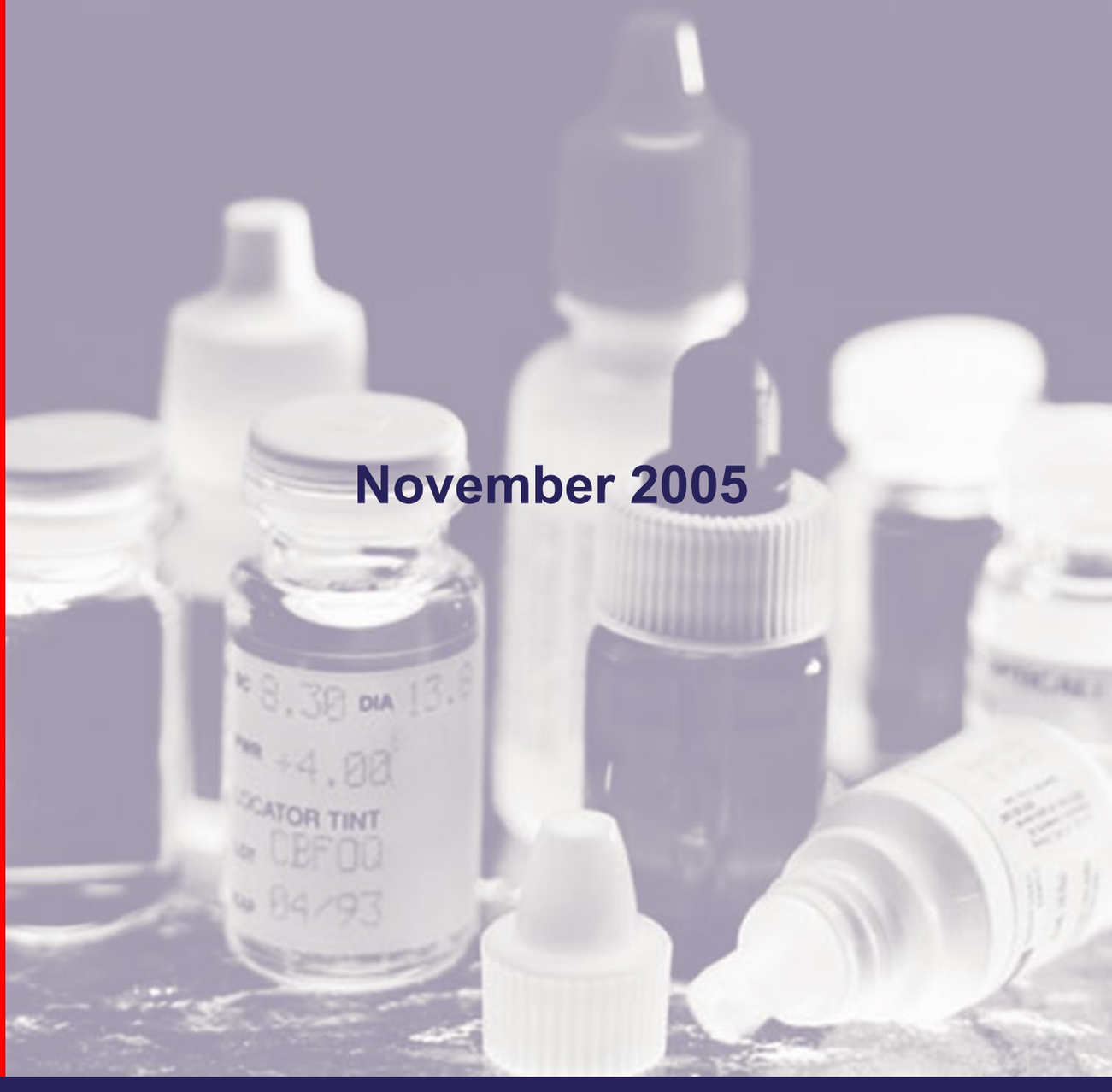
National Cancer Institute

Rapid Access to Intervention Development Program
Developmental Therapeutics Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute

Report of the Workshop To Review the National Cancer Institute's Rapid Access to Intervention Development (RAID) Program



November 2005

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Contents

Developmental Therapeutics Program (DTP) Rapid Access to Intervention Development (RAID) Program: Summary of Current Process

The RAID program is designed to facilitate translation of novel, scientifically meritorious therapeutic interventions originating in the academic community to the clinic. It makes available to the academic research community, on a competitive basis, National Cancer Institute (NCI) resources for the preclinical development of drugs and biologics. RAID is intended to remove the most common barriers between laboratory discoveries and clinical trial entry of new molecular entities.

Services

RAID is designed to accomplish the tasks that are rate limiting in bringing discoveries from the laboratory to the clinic. Once a project has been approved, NCI staff members interact directly with the principal investigator (PI). NCI contractors perform RAID-approved tasks under the direction of the NCI staff. In the event of licensure to an eligible small business, the licensee can participate in project meetings with the permission of the PI, but the NCI will at all times consider the PI the main point of contact for the project. Specific tasks necessary to accomplish in each case will vary from project to project. In some cases RAID will support only the one or two key missing steps necessary to bring a compound to the clinic; in other cases it may supply the entire range of development tasks needed to file an Investigational New Drug (IND). Examples of tasks that can be supported by RAID include, but are not limited to:

- Definition or optimization of dose and schedule for in vivo activity
- Development of pharmacology assays
- Conduct of pharmacology studies with a predetermined assay
- Acquisition of bulk substance (good manufacturing practices [GMP] and non-GMP)
- Scale-up production from lab scale to clinical trials lot scale
- Development of suitable formulations
- Development of analytical methods for bulk substances
- Production of dosage forms
- Stability assurance of dosage forms
- Range-finding toxicology
- IND-enabling toxicology, with correlative pharmacology and histopathology
- Planning of clinical trials

- Regulatory affairs, so that U.S. Food and Drug Administration (FDA) requirements are likely to be satisfied by participating investigators seeking to test new molecular entities in the clinic
- IND filing advice (RAID does not prepare the IND application.)

The output of RAID activities will be both products and information that will be made fully available to the originating investigator for support of an IND application and clinical trials.

Eligibility

RAID is intended for use by academic discovery laboratories and not-for-profit organizations. Most applicants for activities funded by RAID will have an appointment in an institution with an NIH-assured institutional review board (IRB) or formal collaborations with a staff member of such an institution. Projects arising solely from a corporate source without academic collaborators are not eligible.

Application Process

The NCI receives proposals twice per year. Proposals consist of an application, a technology transfer form, and, if required, a letter of commitment from the investigator's institution indicating support for the clinical trial. Applications are NOT expected to request specific funds or even estimate costs. A central function of the NCI staff in the RAID review process is to outline costs utilizing U.S. Government internal or external contract sources to achieve the desired goals.

Review Process

Requests are reviewed by a specially constituted RAID review panel consisting of outside experts from academia and industry. NCI staff members participate in an advisory capacity, not as voting members of the panel. RAID review panel members are bound by confidentiality agreements customary for review of NIH grants.

Current review criteria include:

- Strength of the hypothesis
- Novelty
- Costs and benefits
- Feasibility

What RAID Is Not

- RAID is not an unconditional commitment to develop a particular compound for the clinic. Development will proceed sequentially in a logical order, and the start of one segment of the process (e.g., toxicology) will depend on satisfactory completion of preceding segments (e.g., formulation). Insurmountable difficulties in one segment may force the abandonment of individual projects, as they do in any development program.

- RAID is not intended to assist industry in its development projects in the absence of an academic partner.

- RAID is not a grant program to a particular laboratory. It is expected that the majority of resources committed through RAID will be through use of NCI new-agent development contracts and of NCI staff expertise in service of highly meritorious projects originating in academia. The focus will be on using NCI staff expertise to define the most effective and cost-efficient means of accomplishing the necessary tasks.

- RAID is not intended to support the provision of materials for Phase II and III clinical trials.

THE UNIVERSITY OF TEXAS
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Office of the President

November 2, 2005

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Dear Drs. Barker and Doroshow:

As Chair of the Committee to review the National Cancer Institute's Rapid Access to Intervention Development (RAID) Program, I am pleased to submit our final report.

Sincerely,

John Mendelsohn

John Mendelsohn, M.D.
President

Enclosure

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July 13, 2005

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Workshop Agenda

July 13, 2005

Bethesda Marriott
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7:15 a.m. - 8:00 a.m.	**Continental Breakfast**
8:00 a.m. - 8:10 a.m.	**Background, Meeting Overview, and Introductions** Anna D. Barker, Ph.D.
8:10 a.m. - 8:30 a.m.	**Meeting Goals, Process, and Outcomes** **Plan for Report—Assignments** John Mendelsohn, M.D., Chairman*
8:30 a.m. - 9:15 a.m.	**RAID in Context: The NCI's Drug Development Program** *(10-minute discussion)* James H. Doroshow, M.D.
9:15 a.m. - 10:15 a.m.	**The RAID Program: History, Candidate Selection, Funding, and Management** *(30-minute discussion)* Joseph E. Tomaszewski, Ph.D.
10:15 p.m. - 10:30 a.m.	**Break**
10:30 a.m. - 12 noon	**Outcomes/Productivity of the RAID Program** *(45-minute discussion)* Joseph E. Tomaszewski, Ph.D. Stephen P. Creekmore, M.D., Ph.D.
12 noon - 1:15 p.m.	**Lunch** *(60-minute executive session and then break into groups)*
1:15 p.m. - 3:15 p.m.	**Two Work Groups (Biologics and Small-Molecules)** • Progress Assessment • Future of RAID—Development of Recommendations
3:15 p.m. - 3:30 p.m.	**Questions and Answers for the NCI Staff**
3:30 p.m. - 4:00 p.m.	**Group Reports (Guidance Questions)**** **Summarize Assessment and Recommendations**
4:00 p.m. - 4:30 p.m.	**General Discussion**
4:30 p.m. - 5:00 p.m.	**NCI Response—Followup** Anna D. Barker, Ph.D., and James H. Doroshow, M.D.

*Discussions led by Dr. Mendelsohn
**Presentations by work group reporters

Review Committee Objectives

1. Develop an understanding of the NCI's RAID Program through a review of documents, presentations, and discussions that describe the program, including goals and processes for application, review, and selection of successful candidates.

2. Assess the value (outcomes/productivity) of the RAID Program based on appropriate benchmarks that capture the intent of the Program.

3. Assess the overall return on investment of the RAID Program to date.

4. Offer recommendations to NCI leadership as to the future and/or future directions for the RAID Program in the context of the Institute's overall drug/biologics development program.

Guidance Questions for the Committee

Overall Assessment

- Has the RAID Program met its goals?
- If so, what is the overall value added (specific examples of productivity in the production of high-value products that reached clinical trials)?

Application, Review, and Selection Process

- Are the RAID application and review processes designed to attract the best candidates, and, specifically, are the reviews balanced to achieve the goals of the program and optimize the investment of resources?
- What modifications to the current project acceptance criteria are required? What stages in the drug development continuum should receive the highest priority?

Oversight and Management

- Is the oversight, prioritization, and two-tiered active program review process sufficiently robust to ensure that the best candidates are developed?
- Deciding to continue to invest in the development process for a biologic and/or small molecule is generally based on milestone achievement and, in the private sector, on a series of other factors. How can the RAID Program better evaluate projects, and what should the discontinuation criteria be?

Focus

- Biologics have been a major focus of the RAID Program. Was/is that an appropriate strategy for the future?

Investment

- Is the level of investment in RAID appropriate? Should it be higher or lower?
- Has RAID produced an acceptable return on investment?
- Are new public/private partnerships needed to help fund RAID? If yes, propose mechanisms.

Future of RAID

- The current RAID Program began in 1998; should it continue? If so, what should change, if anything?
- Are there other forces that will produce additional demands for a RAID-like program sponsored by the NCI?
- Is the RAID Program investing enough to achieve success, or does success depend as much on process and management as on money?
- Should more funds be allocated to RAID? If so, what priorities will be critical investment areas in the future?

Additional Questions To Consider

How can the NCI and the RAID Program reach out to investigators to make certain that the highest value projects receive an appropriate evaluation by the Program? Or what outreach programs should be developed by the NCI and the RAID Program to make certain that investigators with high-value projects apply to the Program for resources?

What metrics should be used to evaluate the success of the Program, number of projects completed, number of IND applications filed, number of patients treated, etc.?

Should the RAID Program concentrate on specific agents that may receive a very narrow clinical evaluation as has been done in the past, or on the production of reagents that can be used by many investigators? Or on the refinement of vectors for comparative purposes?

Should the NCI assist with the filing of an IND application or the conduct of clinical trials to a greater degree than originally planned?

Report of the Workshop To Review the NCI's RAID Program

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Summary

The NCI's RAID Program is successful by many criteria. Its strong points include a talented and experienced senior staff, achievement of proof-of-concept at a reasonable cost (28 agents available for clinical trials and 24 IND applications), and a demonstrated willingness to tackle many complex, first-in-class technologies.

The track record is less impressive with regard to the actual movement of new agents into clinical trials. This may be attributable in part to the short life of the Program (7 years) but also points up the need to shift the vision from provision of new drugs for clinical exploration to actually entering new drugs into first-in-human clinical trials. This shift in vision was clearly articulated in the presentations to the committee made by NCI senior leadership, who also presented analyses of ways to improve prioritization, establish milestones, and adhere to timelines.

The leaders of the RAID Program also provided a 7-year summary of activities in the Program, including review procedures, metrics, and numerous examples of issues that impeded success or caused substantial delays.

The informative reports provided by the NCI will not be reviewed in their entirety in the report of this committee but should be attached to it, because they provide valuable background and data that were critical in the committee's deliberations.

The committee's recommendations are presented below. There are three major themes.

- The criteria for accepting a RAID proposal should include a commitment by the investigator to bring a new anticancer agent into a first-in-human clinical trial, with guidance from the RAID staff or through formal collaboration. The focus needs to be less on the investigator and more on achieving a clinical trial as the endpoint.
- Based on what has been learned, RAID Program oversight committees for small molecules and for biologics should perform more active progress reviews by monitoring milestones and achievement of timelines and interceding with changes in course or with "no-go" decisions when appropriate. Project managers accountable to RAID leaders and the oversight committees should proactively advise the PI on the steps necessary to move forward. Project managers should be empowered to intervene when recommendations from the oversight committees are not followed and oversee the performance of contractors who are paid to carry out specific assignments within the project.
- Since the technologies for new drug and marker development are becoming complex and since highly qualified leadership and peer review groups are difficult to enlist, the committee strongly endorses the NCI's consideration of pursuing new drug development in its internal and extramural programs within a single oversight and portfolio management structure. Collaboration, sharing of best practices, and prioritization are critical today. Skills and expertise in the leadership and in the review committees of the extramural and intramural programs should be blended

whenever this will streamline oversight, improve research quality, and enhance achievement of successful outcomes that provide new therapies for patients with cancer.

Committee Activities

The committee to review the NCI's RAID Program met for a full day in Bethesda on July 13, 2005, under the leadership of John Mendelsohn. Two panels were created, one for small molecules chaired by William N. Hait with Robert A. Kramer serving as reporter and the other for bologics chaired by Louis Weiner with John W. Park serving as reporter.

The day's activities involved presentations from the NCI leadership to the committee with an opportunity for questions, separate meetings of the two panels, and a meeting of the committee to begin to synthesize recommendations. Detailed minutes of the committee meetings were provided by the NCI staff, and summaries of the individual panel meetings were provided by the reporters.

Each panel met subsequently by teleconference, joined by the committee chair and NCI leaders.

Draft reports from the panels on small molecules and biologics were submitted for review and were discussed at a teleconference that included NCI leaders, the committee chair, and the panel chairs and reporters. The committee report was drafted by the chair and circulated to NCI leaders and committee leaders for comments and suggested revisions.

Background Information Presented by the NCI Staff

The RAID Program is located in the NCI's DTP. It provides access to unique drug development resources not commonly available to extramural investigators in academia and nonprofit organizations. The goal is to bridge the gap from lead discovery to provision of the drug for clinical trials, helping external PIs and their institutions carry out both preclinical development and clinical research. Funds are allocated for producing and testing a novel agent in quantities needed for preclinical studies and clinical trials and for altering lead compounds and delivery systems to achieve optimal activity and formulation. This is carried out typically through a series of subcontracts to companies with the required expertise.

The first round of applications was received in September 1998. Since the Program's inception, 288 applications have resulted in 104 approvals. Fifty-eight of these projects are completed or discontinued, with a median time to completion of 24 months for small molecules and 31 months for biologics. By the end of 2004, 28 agents were available for clinical trials, and 21 had been licensed. These include roughly two-thirds small molecules and one-third biologics. There were a total of 24 INDs, but the number of patients entered into clinical trials was fewer than desired. The expenditures were $74.3 million in contracts, averaging $12 million per year.

The other main extramural funding source from the NCI for new agents is the National Cooperative Drug Discovery Group (NCDDG) Program, dating back to 1984. Funds are awarded as grants to the PI, for whom the NCI staff provides counsel and review of progress. Drug development to the point of clinical trials is

planned by the PI and his or her institution, with advice from the NCI staff. The NCDDGs have produced 15 INDs and 4 new drug applications, which resulted in FDA-approved drugs and biologic agents. The expenditures to date amount to $210 million, averaging $11 million per year.

The NCI extramural drug development effort in the Division of Cancer Treatment and Diagnosis (DCTD) includes the DTP's NCDDG and RAID Programs, along with R01, P01, and SPORE grants focusing on cancer drugs. NCI drug development in the intramural program involves the Center for Cancer Research (CCR) and others, such as the Division of Cancer Biology.

A Drug Development Group oversees development of new therapies for which the NCI holds the IND. These can come from the intramural programs, academic laboratories, or industry. The services provided in drug development are similar to those provided for development of new drugs in the RAID Program. They include screening, synthesis, formulation, toxicology, and efficacy testing of both small molecules and biologics. The work may be carried out by contractors or by NCI scientists at Frederick, Maryland.

The separation of extramural and intramural drug development, which resulted in part from the review of the NCI in 1998, has produced clarity in the chain of command and enhanced NCI support for extramural academic, not-for-profit, and small-business investigators. However, it appears that this may dilute the efforts and availability of the small cadre of NCI employees with expertise in drug development who can prioritize, facilitate, and provide wise counsel. In addition, it appears to have produced some redundancies in oversight and allocation of NCI resources for drug development.

RAID Review Process

The review processes for RAID proposals involving small molecules and biologics differ. Both are two tiered, with an initial scientific review followed by a second technical review focusing on feasibility and prioritization. For biologics, this entails review by two different committees. The first is a peer review committee that has continuity. The second is a Biological Resources Branch Oversight Committee, which reviews intramural (primary review and technical review) and extramural (second-level technical review) biologics proposals.

For small molecules, the first level of review is provided by two ad hoc experts, and the second review level is provided by an ad hoc peer review committee of experts that does not have continuity, so prioritization in an ongoing way is not possible.

Thus, the biologics area provides more complete oversight, with opportunity to compare and prioritize proposals over a period of time.

Primary review criteria include strength of hypothesis (40%), novelty (40%), and costs and benefits (20%).

It was pointed out that carrying out the 104 projects overseen by the RAID Program has involved work by many hundreds of contractors. The mechanism for selecting contractors is through SAIC, which holds the National Institutes of Health contract to run the Frederick facility. The NCI staff members with the

RAID Program and the DCTD appear to have little control over the selection and oversight of the contractor, the speed with which contracts are let, and the quality review of data produced by the contractor.

It also was pointed out that the initial review process and followup reviews, which consider additional funding and recommend “go, no-go” decisions, have been relatively lenient up to now, tending to favor additional resources for projects where investigators are enthusiastic about publishing their results and exploring further. Some projects ultimately benefited from this, but others remained unpromising in spite of repeated reinvestments. Examples of challenges that delayed progress include incorrect base sequences in plasmids provided for gene therapy, unanticipated problems in solubility, and nonspecificities that had not been detected.

Internal Reassessment of Drug Development at the NCI

An NCI internal reassessment has concluded that there would be benefits in the commingling of scarce expertise from intramural and extramural sources on scientific and technical review panels. The extramural DCTD and intramural CCR have signed a memorandum of understanding to collaborate in developing a clinical target assay laboratory, molecular imaging facilities, and an enhanced infrastructure for clinical trials at the NIH Clinical Center. The latter could support trials from both NCI investigators in the CCR and extramural investigators in academic and not-for-profit institutions. The NCI is developing new laboratories for preclinical molecular toxicology and pharmacodynamic assays for compounds for which the NCI holds INDs, and these resources could be extended to extramural investigators.

Furthermore, the NCI has decided to capitalize on the FDA’s new exploratory IND mechanism and will promote the concept of Phase 0 “pilot” first-in-human clinical trials. These would reduce (but not eliminate) the requirement for preclinical experiments in nonhuman animal models, which have an irregular track record for predicting clinical utility and toxicity, and would allow more rapid introduction of new agents into carefully designed clinical trials. These trials would include collection of pharmacodynamic and pharmacokinetic data; assays of activity on putative targets to assess biological effects and to identify potential markers; imaging; and molecular expression screens to detect changes in gene expression at the levels of RNA and proteins. The goal would be rapid throughput, with collection of data that would inform subsequent Phase I and II trials. The source of agents for these trials could include the CCR and academic institutions.

The committee supported the plans for reorganization and program integration by the NCI and the proposal to make the Clinical Center available for Phase 0 clinical trials.

Issues Raised and Recommendations

The committee identified key issues facing the RAID Program and developed recommendations to address them.

Issue

1. The RAID Program has been investigator oriented. It was established to enable extramural researchers to utilize the NCI's extensive resources for developing new cancer therapies. Experience has shown that this is very beneficial for enhancing the progress of some, but not all, investigators. Many academic researchers are more focused on the molecular and biological questions, rather than on therapy, and have little experience in drug development. Furthermore, academic advancement typically depends on research in molecular and biological mechanisms, supported by peer review grants (especially the time-honored R01) and not on time invested in work with contractors and biotech/pharmaceutical companies. The NCI RAID staff currently has no influence over the investigator's delays and detours related to these issues, which may be for prolonged periods of time.

Recommendations

1.1 Rather than continuing as an investigator-centric program, the RAID Program should become *investigator initiated/investigator friendly* but also *development centric*. Investigators must be required to meet reasonable timelines for productivity, as they would for a typical R01 grant. Having invested in a drug development project, the NCI should have the opportunity to move forward with the project if it appears promising but the PI is not interested in pursuing the project in a timely way. In this situation, NCI administrative leaders should have the options to close the project (currently a "last resort"), write up and publish results (usually data from contractors) for the use of other researchers, or, if intellectual property (IP) issues can be settled, make the agent available to others for further development.

1.2 Information about the experience of the applicant and his or her institution in drug development should be included in the application to the RAID Program. NCI administrative leaders and oversight review committees should provide mentoring and guidance to the investigator and his or her institution when timely progress is not being made. Specific recommendations should be made for further research in the investigator's laboratory to settle preclinical issues, with funding from RAID, which might include partial salary support if necessary.

1.3 The NCI should have the opportunity to collaborate with the PI and his or her institution in planning the initial clinical trials of a new therapy if it appears to be promising and the investigator does not have the experience or resources to plan a clinical trials program. In this case, the IP could stay with the investigator and his or her institution. Alternatively, if a due diligence requirement has been agreed on at the project's initiation, the agent and the IP could be released to the NCI for development or sold by the institution to a biotech/pharmaceutical company if one is forthcoming.

The principle is that if the NCI has invested in developing a promising drug, its further development should not be allowed to stagnate through inaction.

Issue

2. Peer review in the RAID Program is not optimally designed to enable prioritization and review of milestones in conjunction with an agreed on timeline. While the Biological Resources Branch Oversight Committee provides followup on progress with biologics, there is only ad hoc review of this type for small molecules. The current biologics review also has the advantage of examining projects from all relevant sources, both intramural and extramural, making it possible to allocate NCI funds to the most promising new therapies.

Recommendation

2.1 It is suggested that separate, two-tiered review committees be instituted for both small molecules and biologics:

Primary review committee (comparable to a study section). This standing committee would receive three documents for each proposal: (1) the PI's proposal, (2) a timeline and cost estimate prepared by the NCI staff and agreed to by the PI, and (3) an NCI staff estimate of the technical challenges in producing the agent and the pitfalls in moving it forward through necessary testing to reach the clinic. Members of the primary review committee should have the expertise to evaluate these parameters. Ad hoc members may be added to the review committee as needed to provide expertise in novel therapeutic approaches. Each proposal should have at least two primary reviews from the committee to ensure application of expertise in both the science and production technology. The committee membership should rotate periodically as with study sections. Membership of individuals for a period of years will ensure continuity and the ability to accumulate expertise and experience as a group. Priority scores would be given on a scale of 1 to 5, with the anticipation that projects receiving a score of 2.0-2.5 or better would go forward to secondary review by an oversight committee.

Oversight committee. This standing committee would consist of individuals from the NCI, regulatory agencies, and the extramural investigator community and industry who have experience in developing new anticancer agents. This committee would serve two functions: (1) review proposals scored better than 2.0-2.5 in primary review (placing emphasis on feasibility and practical considerations as well as programmatic prioritization goals), seek additional experimental data from the PI if needed, and approve proposals to go forward; and (2) provide oversight and carry out periodic review of progress for the entire portfolio of either small molecules or biologics that are being developed with NCI support, from both extramural and intramural sources. To carry out this function, the oversight committee would examine achievement of predicted milestones and adherence to a reasonable, agreed-on timeline. The committee would provide recommendations for changes in work plans and could intervene with a no-go decision to discontinue development of the

drug, if deemed appropriate. It is understood that this process is in place for biologics. But perhaps the committee needs the benefit of a stronger mandate from senior NCI leadership so that, for the RAID Program, stringency and prioritization in meeting the goal of achieving a clinical trial supersede the interest of supporting exploratory research on a novel scientific approach. The NCI has many other mechanisms to fund the latter type of research.

Issue

3. Very few individuals outside biotech/pharmaceutical companies have broad experience in both research on the biological and molecular pathways that are potential therapeutic targets and the systematic development of a therapeutic agent to the point where clinical trials can begin. Neither the NCI nor academia has many of these individuals on its faculties.

Recommendations

3.1 The NCI staff in the RAID Program (and other programs in drug development) should include adequate numbers of individuals who have the expertise and experience to serve as project managers for developing new cancer therapies. The project managers should follow progress and monitor achievement of agreed-on milestones and should intervene with recommendations to the investigator and the oversight committee when timelines are not met. They should provide both oversight and mentoring for the PI and have the authority to select and oversee the contractors who are paid to perform specific tasks related to developing the drug. Project managers should have adequate staffs to handle administrative tasks so that they can concentrate on managing the maximal numbers of projects. They may command higher levels of compensation than are typical for NIH research administrators, because of marketplace considerations.

3.2 These project managers should meet as a group to exchange best practices and create a policy and technical information manual to assist investigators in drafting proposals. The manual should address IP issues, reasonable times for development, appropriate milestones, and guidelines on the process of obtaining and managing an IND application from the FDA. The manual could be supplemented by workshops (also of interest to investigators outside the RAID Program).

Issue

4. Expertise, infrastructure, and resources are needed for the newly developing concept of Phase 0, first-in-human clinical trials that will provide increased information on effects on targets, identification of potential markers, incorporation of imaging, and sophisticated pharmacokinetic analysis. Few academic centers have ready access to these types of resources and expertise. The concept of using NCI beds in the NIH Clinical Center to make such trials available for new drug development is a tremendous step forward that the committee endorses without reservation.

Recommendation

4.1 The NCI should devise a mechanism supporting collaborative Phase 0 clinical trials in the NIH Clinical Center in which NCI experts offer to work jointly with extramural investigators in the RAID Program (and others) to bring forward first-in-human clinical studies of promising agents as rapidly as possible. This could involve collaboration in dealing with the FDA; completing scale-up, formulation, and preclinical toxicology; designing the optimal clinical trial; and developing and applying assays of molecular effects on targets in malignant and normal tissues. The considerable IP issues would need to be negotiated, and the level of IP sharing may depend on the relative level of resource contribution by the NCI and the academic institution.

Issue

5. Experience has shown that the RAID Program will benefit from more detailed and complete requirements for project proposals and from a more detailed analysis of the investigator's research data and candidate agent prior to commitment of extensive resources.

Recommendations

5.1 Applications should continue to include research data and preclinical information that support moving a proposal forward. In addition, information should be requested in the initial application dealing with commitments by the PI and his or her institution to move the project forward in collaboration with the NCI to achieve entry into the clinic in the shortest practical period of time. Issues to be dealt with include IP; ability and commitment to carry out further experiments in the PI's laboratory (or at his or her institution) when needed to improve the agent or understand its optimal use; and agreement either to design the appropriate clinical trials, with mentoring when appropriate, or to collaborate formally with the NCI or with other cancer centers. There should be a requirement for periodic review to assess progress toward a clinical trial, with the opportunity for the PI to retain control or collaborate with the NCI as the scope of the clinical trials effort becomes clearer.

5.2 NCI administrators and staff members should meet with the investigator as part of the review process to raise technical questions, explore data on efficacy in more detail, and explore practical issues related to formulation, production, and scale-up.

5.3 The NCI should require investigators to submit a candidate agent for analysis of key properties that may require modification, prior to acceptance into the RAID Program. Examples of potentially problematic issues include genes and RNA molecules that must have the correct sequence, vectors for delivering genes and other agents, contaminants that may contribute to observed effects, and verification of activity in more than one cell line or nonhuman animal model.

Issue

6. The metrics of the RAID Program's productivity that have been collected to date are reasonable for a new program in drug development that is less than 7 years old. Fewer than half of submitted projects have been accepted, a reasonable number of licenses have occurred, and INDs have been obtained. As the Program continues, the metrics for evaluation of success should evolve.

   The ultimate measure of success in a program designed to bring new anticancer agents from the research laboratory to the clinic is, of course, regulatory approval of a drug for clinical use in cancer. However, this criterion for success is not satisfactory because it takes so long to be achieved and is so stringent that it could discourage innovation and risk-taking, which are highly desirable.

Recommendation

6.1 As the Program matures, the metric that might best measure its success is the number (percentage) of new agents that have completed first-in-human Phase 0 and Phase I clinical trials. The goal would include early proof-of-concept, by demonstrating target modulation consistent with the proposed mechanism of action of the new agent. If this is agreed on, it will result in a reassessment of resource allocation, increasing the commitment of RAID's funds to coaching or formally collaborating with the investigator to reach Phase 0 and Phase I clinical trials. It also should result in early exploration for molecular markers that predict biological activity and clinical efficacy.

Other Recommendations

7.1 Academic investigators and their parent institutions should receive NIH credit for a RAID award, similar to the credit for NIH dollars from grants and contracts. This is especially important for faculty building academic careers and for universities wishing to qualify for Cancer Center status.

7.2 The NCI should facilitate publication of discoveries made by contractors in the course of developing a new anticancer agent so that new methodologies can be shared and pitfalls can be avoided by others. Agreements on authorship and responsibilities for publications should be made between the NCI and RAID investigators early in the process of activating an award.

7.3 Mentoring and advice should be provided by NCI project managers in all aspects of moving from a lead to an agent in clinical trials, including regulatory issues, IP issues, and best practices in the translation of an agent from an academic laboratory to a biotech/pharmaceutical company.

7.4 At a time of budget constraints, portfolio management and setting of priorities must be adhered to, recognizing that such action may be disappointing to PIs who have invested time and effort.

7.5 The development of drugs for pediatric cancer is a challenging area where the RAID Program can make important contributions.

7.6 The NCI could greatly aid investigators and their institutions by contracting for GMP-compliant storage and distribution of new drugs for which the investigator's institution holds the IND.

7.7 The committee members identified the need for toolkits that provide researchers with unique agents and reagents that would otherwise be unobtainable. Examples include a particular cytokine or antibody produced in scaled-up quantities by the RAID Program or a novel vector developed in the context of research contracted by the RAID Program. While this was felt to be highly desirable for use in the research community, it was recognized that provision of such reagents for general research purposes goes beyond the mission of the RAID Program. It is hoped that resources to support such an initiative can be identified.