

NCI RADIATION RESEARCH PROGRAM MEETING REPORT

YOUNG INVESTIGATORS WORKSHOP—RADIATION RESEARCH PROGRAM, RADIATION ONCOLOGY SCIENCES PROGRAM, NATIONAL CANCER INSTITUTE, NIH, AUGUST 1–2 2000

PREPARED BY THE WORKSHOP PARTICIPANTS AND C. NORMAN COLEMAN, M.D.

Radiation Oncology Sciences Program, NCI, Bethesda, MD

INTRODUCTION

The one-and-a-half day Young Investigators Workshop was held in the Holiday Inn, Bethesda, August 1–2, 2000. Using the SCAROP mailing list and recommendations from department chiefs, approximately 55 “early-career” physician-scientists were invited to attend the workshop. Table 1 includes the participants.

The goals of the meeting were:

- To bring together radiation oncology physician-scientists who were in the early part of their career to discuss research ideas and opportunities as well as potential barriers to progress for the field and for young-investigator careers.
- To help develop camaraderie among and a critical-mass of a new generation of physician-scientists with interests ranging from technology development, to basic and translational research, to outcomes research and analysis.
- To help the young investigators gain familiarity with the NIH grant programs.
- To prepare a “white paper” with their vision and ideas for potential opportunities for the future. If possible, a short- and long-term agenda were to be proposed.

The first morning included presentations from a variety of NCI programs. Three breakout sessions were held in the afternoon. Breakout Group Reports were discussed by the entire group the following morning. A fourth discussion topic on “Barriers To a Successful Research Career” was conducted by the entire group. Drafts of this entire Workshop Report were circulated to the participants. The final document represents the efforts of the entire Young Investigators Workshop and provides the perspective from the point of view of the investigators who have many years to invest in the future of radiation oncology.

The Radiation Research Program (RRP) is grateful to all the participants for a lively workshop and to the session co-chairs for the timely preparation of this report.

BASIC BIOLOGY

For decades, radiation oncologists in the clinical arena have forged new frontiers in the combined-modality approach to cancer. From organ-preservation using chemoradiation to intensity-modulated radiation therapy, radiation oncologists have significantly improved cancer cure rates in concert with a multidisciplinary clinical team. The members of the Basic Biology Committee of the Young Investigators Workshop recognize that today’s radiation therapy must harness our ever-expanding understanding of the molecular pathogenesis of cancer. We stated, unanimously, that basic research into the biologic sciences will change the future clinical practice of radiation therapy and impact on patient survival. It is incumbent upon us to stress to the radiation oncology community that existing Phase I and II clinical data support the impact of molecular biologic strategies on improved patient outcome. Positive clinical trials using anti-epidermal growth factor receptor (EGFR) antibodies, p53-gene therapy, ras inhibitors, and Herceptin are the product of basic science researchers translating their increasing understanding of molecular biology to improve clinical care for cancer patients. Our task in the Basic Biology Committee was to delineate our vision of the key goals for the radiation oncology community. These goals are:

1. To elucidate the determinants of radiation response in normal and neoplastic tissues
2. To establish the determinants of tumor initiation, maintenance, and progression
3. To achieve a molecular and genetic classification of tumors and individualization of therapy

New treatments for cancer have historically appeared as likely panaceas. We recognize that lineage and tissue-specific differences among tumors may impact on the relative importance of each biological determinant and clinical application. We further recognize the complexity introduced by intra- and inter-tumoral heterogeneity.

Table 1. Workshop participants*

Basic Biology	Imaging and Physics
Daphne Haas-Kogan*	Thomas Merchant*
Robert Bristow*	Monica Morris*
Amit Maity*	Jacques Balosso
John Anderson	Roscoe Chan
Claus Belka	Jay Ciezki
Arnab Chakravati	James Brian Davis
Theodore Chang	Ronald Ennis
Paul Cornes	Gary Freedman
Ken Dornfield	Cai Grau
Steven Howard	Larry Marks
Mohamed Khan	Nina Mayr
Chandan Guha	Andrea Ng
Carolyn Sartor	Ken Rosenzweig
Matthew Spear	Sandra Russo
Craig Stevens	Bin The
Marcel Verheij	
Li-Xi Yang	
Michelle Yao	
Biological Applications	NCI participants
Michael O'Reilly*	Norman Coleman
Stephan Bodis*	Richard Cumberlin
Judith Ford*	Frank Mahoney
Theodore DeWeese*	Helen Stone
William Blackstock	Kathy Horvath
Lisbeth Boersma	Frank Govern
Yuhchayau Chen	Jim Mitchell
Brian Collins	Ellen Feigal
Philippe Coucke	Jill Johnson
Steven DiBiase	Diane Bronzert
Adam Dicker	Andrew Vargosko
David Gius	
Chandan Guha	
Donal Hollywood	
Richard Hudes	
Ellen Jones	
Andrew Kennedy	
Quynh Le	
David Raben	
Samuel Ryu	
Jann Sakaria	
Tim Shafman	
Gordon Watson	
Li-Xi Yang	
Barriers to a Successful Career	Graphics
Ted DeWeese*	Adam Dicker*
Tim Shafman*	Norman Coleman*
Entire Workshop	Richard Cumberlin*

* Co-chairperson who drafted the Breakout Group's report

In setting goals for radiation oncologists as scientists we outlined four broad topics:

- I. Basic biologic mechanisms
 - A. The cellular response to radiation
 - B. Normal tissue effects
 - C. Tumor-host interactions
- II. Novel methodologies required to apply our improved understanding of basic biologic mechanisms

- A. Genomics/proteomics based on primary tumor and normal tissues, pre- and post-radiation
- B. Delivery of biological modifiers
- C. Model systems relevant to specific tumor sites
- III. Clinical applications we foresee as the ultimate benefit from basic science discoveries
 - A. Molecular classification
 - B. Novel therapeutics
- IV. Resources required by individuals, departments, institutions, and organizations to accomplish our goals
 - A. Relevant tissue-bank specimens
 - B. Access to human genome database
 - C. Bioinformatics and biostatistics
 - D. Interdisciplinary collaborations

Basic biologic mechanisms

Cellular response to radiation. The cellular response to radiation perhaps most directly relates to radiotherapy. Intense investigation has focused on various modes of cell death, particularly that of apoptosis. The last decade has seen a steady increase in our identification of regulators of apoptosis, such as p53 and Bcl-2, as well as regulators and effectors of apoptosis, such as caspases. Cell origin and lineage are major determinants of the cellular susceptibility to apoptosis. Cells of lymphoid origin are more prone to undergo radiation-induced apoptosis, while cells of glial origin are extraordinarily resistant to radiation-induced apoptosis. Despite a large body of preclinical data, tumor-specific levels of radiation-induced apoptosis in patients undergoing radiotherapy are lacking; therefore, significant disagreement exists regarding the relative importance of apoptosis in determining tumor response and clinical outcome. In spite of this, the committee agreed that novel strategies designed to enhance tumor cell apoptosis are likely to improve clinical outcome.

Although cell death may be the ultimate fate of an irradiated cell, multiple molecular processes characterize the cellular response to radiation. These include cell cycle checkpoints, repair of DNA damage, membrane responses, activation of signal transduction cascades, and induction of senescence/differentiation. Within the field of the cellular response to radiation, basic science discoveries have already led to promising clinical applications. For example, signal transduction provides the bridge between basic biology and pharmacology, and it is through an improved understanding of the former that we should be able to develop biologic agents that modify the radiation response. Two specific examples of pharmacological manipulations currently being tested clinically are farnesyl-transferase inhibitors that block ras function and antibodies against the EGFR.

Normal tissue effects. Radiotherapy may cause serious acute and late toxicities. Therefore, it is critical to extend research on the cellular response to radiation to normal tissues. Understanding the response to irradiation at a molecular level will likely lead to improvements in the therapeutic ratio. Improved understanding of the molecular response of normal tissues may be harnessed not only to

prevent toxicity but also to reverse late effects with stem-cell transplantation, as has been initiated using transplanted hepatocytes to ameliorate radiation-induced liver damage in animal models.

Tumor-host interactions. Evidence of tumor—host interactions in cancer continues to expand. Tumor growth is intimately connected with normal tissues in the host, including endothelial cells, parenchymal tissues, and the extracellular matrix. These tissues communicate by direct contact via adhesion molecules and by paracrine factors. Examples of tumor—host interactions now understood to play key roles in tumor development include angiogenesis and metastasis. Elucidation of molecular regulators of tumor—host interactions has led to the rapid emergence of therapeutic agents targeting these pathways. Current clinical trials have set the stage for a critical evaluation of anti-angiogenesis agents and inhibitors of metastasis.

The novel methodologies required to apply our improved understanding of basic biologic mechanisms

We identified key novel methodologies required to apply molecular studies to radiation biology and clinical practice. These include genomics/proteomics based on primary tumor and normal tissues, pre- and post-radiation; delivery of biologic modifiers; and model systems relevant to specific tumor sites. Over the past year, we have witnessed completion of the Human Genome Project and expansion of DNA microarray technologies, all of which are poised to revolutionize the interdependence of basic science and clinical practice. DNA microarrays have allowed “molecular classification” of non-Hodgkin’s lymphomas and identification of patterns of gene expression that refine clinical prognosis. Using such novel technologies, radiation oncologists can extend these studies to explore gene expression patterns following irradiation and exploit such “molecular classification and target credentialing” for sensitization of tumors and protection of normal tissues.

Clinical applications we foresee as the ultimate benefit from basic science discoveries

Molecular classification. The inspiration for our efforts as clinician-scientists arises out of our confidence that today’s laboratory discoveries will improve tomorrow’s patient care. We recognize the need to keep pace with the rapid development of molecular biomarkers that pertain to the prognosis of cancer, and to the radiation response of cells. These biomarkers should be accurate, undergo rigorous quality control, be surrogates for known clinical endpoints, and be relevant to the clinical setting and individual patient. Many standard treatment strategies in radiation oncology are currently based on results of Phase III randomized trials, which treat large groups of patients assigned different treatments at random. Further benefits in local control and survival may stem from the use of more individualized therapy, as well as risk stratification and staging based on novel biological information.

Future endeavors in predictive assays must be tumor-spe-

cific, given the inherent differences in the cellular and molecular response of human tissues to ionizing radiation. Molecular biomarkers suggested on the basis of *in vitro* biochemical studies should be validated within relevant *in vivo* preclinical models, in order to ascertain altered expression secondary to tumor heterogeneity and variable microenvironments. Furthermore, a multifactorial approach to bioprognostication is currently required, whereby both microenvironmental and intrinsic cellular factors can be modeled in unison to complete a predictive profile for each patient. Such a rigorous approach, incorporating both tumor and normal tissues, may define a “molecular therapeutic ratio” for individuals receiving radiotherapy and guide the treatment plan.

The radiation oncologist will soon benefit from advances in molecular classification and staging of tumors. Genetic and metabolic markers, in conjunction with standard radiographic studies, may delineate the exact location of microscopic tumor. This may alter GTV and CTV volumes and culminate in a “biological target volume” (BTV) that will guide biological and anatomical conformal radiotherapy.

Novel therapeutics. 3D-CRT and IMRT provide anatomical specificity. Molecular therapies will complement anatomical specificity by targeting biological pathways that are dysregulated in individual tumors. The future of radiation oncology will be broadened by the use of radiation in conjunction with molecular therapies that include targeted gene therapy, tumor vaccines, signal transduction modifiers, radioprotectors and sensitizers, and stem cell transplantation. At present, gene therapy strategies, such as adenovirus-mediated p53 delivery, have been utilized in Phase I trials. Randomized trials are underway to determine whether anti-angiogenesis strategies increase the therapeutic ratio. Many questions remain regarding the use of tissue-specific promoters, tumor cell specificity, gene dosage achieved in oxic and hypoxic cells, bystander effects, and appropriate vector-gene combination in a given disease site. The use of novel radiation-responsive constructs in regulating the sustained expression of exogenous therapeutic genes in an irradiated volume is attractive and currently under active investigation.

Resources required by individuals, departments, institutions, and organizations to accomplish our goals

A gap persists between basic laboratory investigations and the subsequent rapid and relevant application of this information in the clinic. Resources to accelerate this transition were delineated: initiation of relevant tumor banks to test radiotherapy biomarkers, increased access to radiobiology and cancer bioinformatics, increased opportunities for industrial collaborations, and an increased need for multidisciplinary cross-cultivation. Resources relevant to radiation are required, including tissue banks of nonirradiated, irradiated, normal, and tumor tissues for each individual disease site.

A more aggressive approach should be taken toward improving collaborations with the pharmaceutical and biotechnology industry to utilize novel therapeutics, which may augment the effects of radiation therapy. A more active

role by radiation oncologists in identifying the most promising agents may be beneficial in new ventures with pharmaceutical collaborations. Interdisciplinary collaborations include the surgeons, medical oncologists, and immunologists in the clinical realm and the molecular biologist and radiobiologist in the laboratory arena. As radiation oncologists, we serve the patient of today; as clinician scientists, we serve the patient of tomorrow.

BIOLOGICAL APPLICATIONS

A wide variety of topics that were relevant to biologic applications of radiation therapy were discussed. The discussions emphasized a need for better integration with physics and biology, with the goal being to improve translation of concepts into the clinic and to stimulate future basic science and clinical research within our field. Many members of the group were concerned that radiation oncology is falling behind in both basic and clinical research relative to other disciplines within the field of oncology. Radiation oncology has fallen behind in the development of new molecules and, as a result, pharmaceutical and biotechnology companies with new molecules favor the medical oncology community, leaving radiation therapy as an afterthought. To correct the situation, we need to take the initiative. Although there has been much technical progress within radiation oncology, the future may very well lie in biologically based therapeutics. Although no specific solutions to these problems were proposed, several issues were addressed, as outlined below.

Endpoints

One of the keys in developing new therapies will be the determination of their efficacy as compared to existing modalities. However, classical endpoints such as tumor response and survival, although necessary, may not be optimal in the determination of the efficacy of some new modalities. The use of survival as an endpoint is further limited by the length of time required, which may limit the efficient development of new techniques and treatment strategies. In the case of combination therapies, endpoints are needed that can determine the relative contribution of the radiation therapy. In addition, surrogate endpoints that can reliably predict for the development of late toxicity are needed. Thus, new surrogate endpoints are needed within the field of radiation research so that the biological modulation of the radiation effect can be quantitated and new concepts can be generated and evaluated.

Surrogate endpoints could help to determine a molecular basis for response. Surrogate endpoints may be derived from several disciplines, including molecular biology and imaging. However, a variety of molecular and imaging methods will be needed, and in most cases no single surrogate will suffice. To test and characterize proposed surrogates, baselines are needed, and we need to compare these markers show with radiation alone before we can use them to interpret the results of combination therapy.

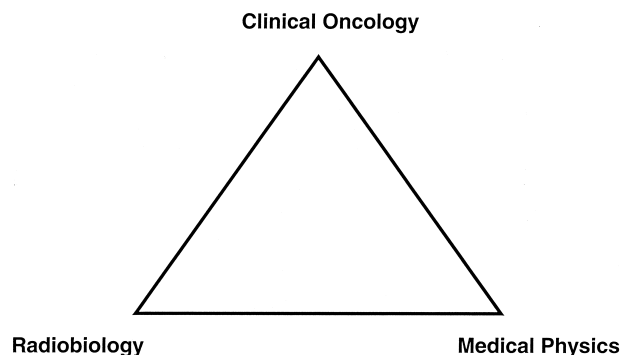


Fig. 1. Conventional training in radiation oncology. The field currently includes three major components. Clinical oncology encompasses natural history of disease, and the various forms of treatment with surgery, radiation therapy, chemotherapy, immunotherapy, combined modality therapy, and prevention. Medical physics includes external beam and brachytherapy techniques, along with treatment planning, the use of unsealed sources, radiation safety, radiation protection, and the use of other forms of energy such as hyperthermia and phototherapy. Radiobiology includes cellular and tissue biology, fractionation, radiation modifiers, some concepts in molecular biology, radiation mutagenesis, and carcinogenesis, as well as aspects of basic radiation physics and chemistry.

To validate these endpoints, they will have to be developed and tested in a preclinical setting, and then tested in the clinic with long-term survival studies in large Phase III trials. Although short-term end points must be assessed, long-term follow-up is mandatory. Normal tissue vs. tumor effects will need to be defined both in the preclinical and clinical settings. In particular, late effects, secondary malignancy rates, and quality of life will need to be studied. The ultimate goal will be to determine a molecular basis for radiation therapy. An emphasis should be placed upon the interconnection between the host, tumor, and stromal interactions at the molecular level.

Training and education

Figures 1 and 2 illustrate current conventional training and a new paradigm for future training in radiation oncology. In many instances, there is inadequate, or even an absence of, formal training in molecular biology in radiation oncology. There was a sense that the great surge of interest in molecular biology was tending to come more from medical oncology and surgery rather than from radiation oncology. Several members of our group were very concerned that radiation oncology has been left behind in many areas of biologic research. Without an improved emphasis on and a better understanding of molecular biology in radiation oncology training, the integration of new modalities derived from molecular biology research will be delayed and poorly implemented. One central problem is the lack of exposure to molecular biology early in training. As a result, it is difficult to get people interested in, and adequately trained for, laboratory research. Further, the rapid transit to specialization in radiation oncology means that many talented people

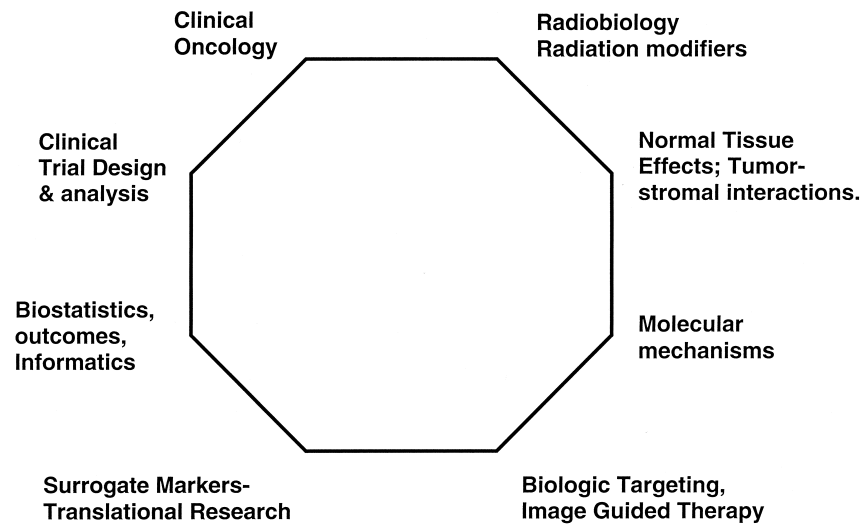


Fig. 2. The new paradigm for training in radiation oncology. Clinical oncology, medical physics, and radiobiology remain the essentials of clinical practice. To be included in future clinical oncology training are economic and health care policy aspects of medical practice. There are numerous ways of dividing the newer knowledge base into its various components, which would include the following: normal tissue tolerance and effects, as taught in radiobiology, but also tumor-stromal interactions and fundamentals of tumor immunology. The molecular mechanisms of carcinogenesis form the basis for understanding new molecular therapeutics. Medical physics would include biological targeting and image-guided therapy. Fundamental knowledge of drug treatment and pharmacokinetics are necessary to bring new molecular therapeutics to the radiation oncology clinic. Clinical trials will be based more on surrogate endpoints and “molecular credentialing” of new drug targets. Biostatistics knowledge would be supplemented by outcomes analysis and the emerging field of bioinformatics, which is necessary to understand how new molecular profiling techniques can be used in patient management. Clinical trial design, conduct, and analysis are essential so that radiation oncology can be a significant participant in bringing new treatments to patients.

are not trained in the skills needed for Phase I and II clinical research with new agents. As a result, others tend to get to take these molecules into the clinic, with the radiation oncologist being forced into a secondary role.

Given the rapid advances being made in the biology of malignancy, training in molecular biology should be improved. The training should begin in medical school, or earlier, and an improved medical school curriculum is needed to better prepare future physicians. In this way, radiation oncology can move away from the perception that it is merely a technical specialty. One possible plan would be to develop alternative tracks for those interested in research within the medical school curriculum and/or radiation oncology residency and/or to establish fellowship programs. These programs may have to be instituted primarily at a limited number of specialist centers, where there would be either a basic science research track with a protected basic science research year reinstated, or a clinical research track with extra training in clinical medicine and clinical trial research. Training should begin as early as possible, and it was suggested that more control over the internship year by the radiation oncology program would result in improved training of radiation oncologists.

Improved training will allow radiation oncologists to be involved in all aspects of cancer care and in all stages of preclinical development. We must be able to take care of cancer patients and their problems if we hope to have a central role in clinical trials. To achieve these goals in the

field of radiation oncology, an effort is needed to attract the best students to the field. Improvements in job opportunities are needed for M.D., Ph.D., and combined programs. An increased role of radiation oncology within the other oncology subspecialties is also needed. Parallel training of resident radiation oncologists with medical oncology would allow for a much broader role in the advancement of cancer care. To have a place in the development of future biologic therapies, we will need to be able to manage the whole patient. Improved clinical training in residency is needed. A variety of short and long-track training options could be implemented and tailored to the needs of the individual. Beyond residency, protected research time for staff radiation oncologists is needed. Refresher training in clinical areas and biological advances need to be developed. The focus of these training sessions will be the translation of new advances into widespread clinical practice. Sponsored time away from one’s institution may be beneficial. Overall, an improved academic output is needed. To achieve these goals, funding will need to be improved. Although research grants exist, specific programs are needed to ensure that there will be enough money for enhanced and improved training throughout the radiation oncologist’s career.

Scientific directions

The main advances in the practice of radiation oncology have centered on the use of other modalities in combination

with radiation therapy. We emphasized the need for cooperation and communication between groups. We thought it would probably be necessary to combine more than one molecular approach with radiation to reap the full benefit, both in the laboratory and in the clinic. Preclinical research needs to demonstrate an effect, but it also needs to determine the therapeutic differential between tumor and normal tissues. An important issue, which came up on many occasions, was the need for long-term followup for late toxicity in all clinical trials. It was suggested that this should include Phase I and II trials, given how long it could be to see late toxicity. It was also thought important that we should standardize reporting of late toxicity.

We feel that current advances and improvements in physics and technology are allowing us to improve our sparing of normal tissues with some increase in dose to tumor. However, if we can use biologic agents to target the tumor and if they can be made sufficiently tumor specific, we can increase our effect on tumor and minimize normal tissue dose and effects. By boosting the tumor with the biologic approaches rather than shrinking the field and adding dose, we may reduce the chance of a geographic miss of malignant disease. A number of new modalities and tools need to be considered. These include antiangiogenesis agents, signal transduction modulators, gene therapy, hypoxia, hyperthermia, molecular imaging, cytokines, monoclonal antibodies, immunotherapy, radiation sensitizers/protectors, immunomodulation, gene profiling, mathematical modeling, microdosimetry, fractionation, and damage repair. In all cases, the systemic effects of radiotherapy will have to be determined. An increased presence for Phase I trials is needed. As newer modalities are incorporated into our field, new methods of evaluation are needed. However, the emphasis should be to determine if new modalities are truly complementary and not just assume that new must be better. A rigorous comparison of new therapies and combinations with existing standards of care is therefore needed. Classical endpoints will be of use, however, other endpoints, such as an emphasis on minimal toxic dose, optimal therapeutic windows, and synergism, are key. The concept of maximum tolerated dose may not be relevant for many new modalities. Multimodality approaches that include biological therapies offer unique concerns. Not only which combination, but also the sequencing, will be critical.

With so many new modalities, priorities will need to be developed. To accomplish these goals, support for focused and well-designed trials and grants is needed. Cooperative clinical trials will allow for the translation of basic research to Phase I, II, and III trials and long-term follow-up will be needed. We should also emphasize the quantitation of dose modifying properties when relevant. SPORE and/or P-01 type grants will be needed to support major research efforts. Preclinical research funding should match the clinical importance and potential clinical benefits of proposals. As part of a research network, standardized scoring systems, a focus on academic pursuits amongst radiation oncology staff, and

central/core facilities need to be developed. A focus on preclinical and clinical targets is needed at all stages.

Public relations

An improved visibility for biological applications in radiation oncology at ASTRO and similar meetings is needed. Abstract reviews would allow for the presentation of novel and significant scientific findings to the radiation oncology community as a whole and would help to generate enthusiasm within the field. Late-breaking sessions and other forums, such as the Presidential address at the annual meeting of ASTRO, should emphasize biologic applications. Increased funding could be tied into these presentations. The dissemination of information for research career opportunities should also be emphasized and standards for successful research should be set. Links to industry for drug development and relevant clinical trials need to be established. A greater emphasis should be placed on organizations that promote studies of basic biology and translational research, such as the Radiation Research Society, should be developed to complement the current focus on the presentation of clinical trials.

IMAGING AND PHYSICS

In the future, physics and imaging research in radiation oncology are likely to focus on the application of biologic techniques and advances in an effort to make additional gains in treatment planning and delivery beyond that which has been achieved using current 3-D treatment planning techniques. The future is likely to see multidimensional (4th and 5th dimensional) treatment planning, where the additional dimensions would include information pertaining to tumor and normal tissue biology and physiology. Beyond treatment planning and delivery, monitoring tumor and normal tissue response to therapy and evaluating treatment failure with respect to treatment dosimetry appear to be valuable areas of pursuit.

There are a number of independent treatment modalities that are included within the realm of radiation oncology, including brachytherapy, external-beam radiation therapy, radioimmunotherapy, hyperthermia, and others. All of these modalities have in common the need for 3D and multimodality imaging technology with applications to include treatment planning, delivery (verification), treatment response, post-irradiation treatment effects, and failure recognition. Normal tissue dosimetry and treatment effects are, in many cases, as important as tumor control.

Radiation oncologists need to work harder to develop relationships with colleagues in diagnostic imaging. These relationships will identify areas of potential research interest to radiation oncologists. At the same time, more independence is needed with regard to imaging technology access (all imaging modalities included), and input from sources outside of the medical field is likely to provide additional opportunities for improving radiation therapy. Outside sources would include information systems, computer pro-

gramming, and engineering subspecialties. There is also an opportunity to borrow from other medical specialties, such as cardiology and surgery, innovations or technical developments that have advanced those specialties and that might also be useful in radiation oncology. Important examples would include stereotaxy, physiologic gating, and real-time image-guided interventions.

Convincing data are emerging that demonstrate the benefit of 3D treatment planning and delivery. Improved local control and reduced acute and long-term side effects appear to be the relevant endpoints. In treatment planning and delivery, many feel that technical developments that involve treatment delivery are more likely to impact radiation oncology than treatment planning. This might include the increased availability of particle therapies, improved localization and verification, and interactive treatment. Countering this point of view would be the application of more sophisticated methods to define subclinical tumor and plan therapy based on improved targeting.

Parallel with the more recent developments in planning and delivery technology has been the discovery that combined modality therapy (i.e., radiation plus chemotherapy) improves outcome over radiation therapy alone for many tumor sites, including the head and neck, esophagus, and gynecologic malignancies. The imaging and physics committee members were concerned that if targeting was not improved or if models for dose and volume effects were not improved, that radiation therapy might be perceived as the more toxic of the two modalities. If this misperception were acted upon by those who primarily manage patients, definitive treatment with radiation therapy might be withheld or delayed, with a detrimental effect on disease control and overall patient care.

Our committee included approximately 12 radiation oncologists representing diverse but academic departments with wide-ranging interests. A wide range of treatment capabilities and research opportunities were also noted. Consequently, technical training could vary markedly among trainees. Additional resources are necessary to train and sustain academic radiation oncologists, as is discussed below in the “Barriers” section.

Workshops to standardize the reporting of results, to develop guidelines for the use of advanced imaging modalities, or to make more consistent use of 3D treatment planning technology were considered as potentially useful. Patterns of care studies were suggested for many anatomical sites and disease entities treated with advanced imaging and physics technology. Pilot studies funding new imaging and physics initiatives were suggested by many of the committee members. Regular meetings to discuss developments in basic biology and biologic applications that might be moved into clinical applications were considered to be necessary. Because there are many similarities between the needs of clinicians and those using preclinical models, experts on imaging of clinical models should be consulted to determine if any of their developments look promising for use in humans.

The group was interested in mentorship, guidance, and/or the development of a mentored course to improve the ability to obtain funding and to obtain access to resources, ideas and developments at the Radiation Oncology Branch of the National Cancer Institute.

1-, 3-, and 5-year plans

During the next year, hypothesis-driven research questions, including new and original ideas, will move beyond the mere testing of new technology. Identification of priority areas and critical issues concerning radiation oncology and the application imaging and physics research are important; with the ultimate goal to make radiation therapy more effective, safer, and easier to plan and deliver. Making new technology more widely available is another important goal.

Over a 3-year period of time, resources might be developed within the radiation research program to aid researchers who wish to pursue questions related to imaging and physics. The development of these resources might parallel those developed within developmental therapeutics for general oncology and biology. Shared software, computer programming, data storage and retrieval, and quality assurance support should be sought. This could be centralized and performed by single or multi-institution contracts.

Within 3–5 years, we would like to see within radiation oncology a small number of institutions identified as Centers of Excellence for imaging together or separate from the cancer diagnostic imaging centers of excellence identified as “P50” and “P20” institutions. Such centers would not replace or displace other investigators, but would enhance the productivity of the overall radiation oncology community by having additional resources available within individual centers or within consortia. This approach is currently being evaluated in diagnostic imaging.

Specific topics of interest involving imaging are:

Pre-irradiation imaging:

Oncology staging, prognostic factors, and baselines

Treatment planning

Tumor definition

Normal tissue definition

Automated planning—segmentation and pattern recognition

Image processing with multimodality registration

Imaging agents and enhancers

Adaptation of instrumentation and sources

Organ motion, gating, and immobilization

Modalities including: fluoroscopy, CT, MR, functional MR, quantitative MR, and MR spectroscopy, nuclear medicine, ultrasonography, megavoltage tomography, biologic imaging-enhancement agents, chemotherapy agents, electron spin resonance

Targeting

Patient motion and organ motion correction compensation

- Real-time or iterative compensation/correction
- Tomotherapy
- CT on rails
- Ultrasound hyperthermia
- Combined magnetic resonance and therapy units (the above used for external beam irradiation or brachytherapy)
- Response
 - Imaging of classical, biologic parameter such as pH and pO₂
 - New biologic imaging technology—genetic tagging
 - Radiosensitizers and enhancers
 - Normal tissue protection agents
 - Chemotherapy agents

Post-irradiation imaging

- Tumor control
 - Tumor failure recognition
 - Patterns of failure analysis
 - Imaging-biologic coordinates
 - Time course of response
- Toxicity assessment
 - Objective measure and normal tissue effects
 - Time course of side effects

NAVIGATING THE OBSTACLE COURSE: BARRIERS TO A SUCCESSFUL RESEARCH CAREER

Success in any endeavor requires careful planning, establishment of realistic goals, and, above all, hard work. Success is also frequently dependent on the assistance, direction, and support of mentors and peers, as well as a stimulating environment. When all of these elements are in place, the probability of success increases. If one or more of these elements are lacking, the likelihood of reaching these goals is diminished. Frequently, many of the obstacles to success can be removed with creative thinking. For others, a map is necessary to identify them and to successfully navigate around them. Success in identifying and navigating the barrier-filled waters is imperative to building and maintaining a sustainable cohort of motivated and capable young investigators. Failure to do so will result in a significant decrement in the quantity and quality of research in radiation oncology and, with it, loss of ownership of the research agenda in the specialty.

The Young Investigators Workshop has identified a number of impediments to a successful research career. The group recognizes that whereas multiple institution-specific obstacles exist, there are a several barriers that are nearly ubiquitous in their occurrence. For organizational purposes, these impediments can be generally categorized into three main areas: institutional, governmental, and educational. Specific examples of barriers in each of these areas will be provided. These examples are meant only to reflect the type of barriers that are perceived to exist. Each barrier or set of

barriers will also be followed by one or more suggestions to address the identified concerns.

Institutional barriers

The workshop members were nearly unanimous in their recognition of several common, institutionally based barriers that affect early research career development. The institutional barrier most commonly identified among members of the group was a lack of direct and structured mentorship. Whereas several members of the group noted that such activity existed at their individual institution, most members stated that they had neither been provided research-career guidance nor were they able to find members of their department eager to provide such guidance. This lack of mentorship was felt to hinder present and future productivity, including the ability to successfully compete for research grant money. This deficit was also felt to limit important contact with scientists and researchers in other departments and the subsequent opportunity for critical collaborative exchange and inclusion in funding opportunities. These significant associations can be facilitated by the department chairperson and/or mentors, attendance at scientific and other research conferences, etc. The workshop believes that this mentorship could also be provided by interested investigators outside the individual institution, perhaps by members of the Radiation Oncology Sciences Program of the NCI. Additionally, a nationwide “clearing-house” could be established by ASTRO and/or the RRS, which would provide a list of established investigators interested in and capable of research career guidance. Individual young investigators must, however, take primary responsibility for involving themselves in this collaborative exchange and elucidating their research ideas and agendas. Finally, the workshop also suggests that ASTRO sponsor structured grant-writing workshops involving appropriate members of the NCI to enhance the ability of young investigators to successfully compete for peer-reviewed grants, particularly those investigators with limited access to appropriate mentoring.

The next most commonly identified institutional barrier was lack of protected research time. Members of the workshop felt strongly that although their chairpersons were generally supportive of faculty research goals, they also were frequently not providing adequate time to pursue these goals. Moreover, it was felt that job descriptions changed over time, with chairpersons imposing additional clinical and administrative responsibilities, adding to the confusion and frustration felt by young investigators. The workshop suggests that a survey of department chairpersons and faculty be performed to determine: (a) the amount of research time thought to be appropriate for a clinical researcher as well as for a clinician-scientist, (b) the amount of time actually being provided, (c) the criteria upon which the amount of time provided is determined, (d) how this time is protected, and (e) what markers are used to determine if appropriate progress is being achieved. In addition, suggestions for and/or response to new models of clinical sched-

ules could be solicited, including the use of “mini-sabbaticals,” titrated clinical time from 1–5 years, job sharing, etc. These data could then be used to begin constructive dialogue between young investigators and their chairpersons as to how their institutional model could be modified to provide enhanced opportunity for success.

It was also noted that the involvement of radiation oncology faculty on large, multi-investigator/multi-project grants, like SPORE grants, is generally poor. Involvement of young investigators on these types of grants would not only provide access to a large, multi-year funding source, it would also expose faculty outside radiation oncology to the type of research being conducted by young investigators. These interactions would heighten the likelihood of sustainable collaboration between young radiation oncology investigators and other investigators outside their department. The workshop suggested that inclusion in such grants could be enhanced by more involvement of their chairperson in the planning phase of such grants and an otherwise proactive stance on inclusion of radiation oncology in these efforts.

Governmental barriers

The NCI has the ability to identify and in certain instances provide set-aside funding to areas of research which it determines are critical to its mission. As an example, the NCI recognizes that the development of cancer chemoprevention agents, as well as more traditional cancer chemotherapeutics, would be facilitated and likely accelerated by the study of early markers of efficacy. As a result, the NCI has issued RFAs in both areas to determine if certain biomarkers can be identified and rationally applied in drug development, thereby diminishing the time over which a drug is tested and determined to be useful. Radiation therapy plays a significant role in the management of patients with cancer at sometime during the course of their disease. As with drug therapies, radiation therapy would similarly benefit by intensive study of early markers of treatment effect, which may also have the potential of altering the manner in which clinical trials using radiation therapy are conducted and interpreted. The Young Investigators Group suggests that the NCI consider a RFA that seeks to identify novel biomarkers of radiation response using *in vitro* and *in vivo* models and then translates these markers to the human. Once translated, these markers will require correlation with several known clinical and/or pathologic outcome parameters and will ultimately serve to provide a molecular profile of a patient suitable for radiation therapy.

Clinical research in radiation oncology frequently requires long-term follow-up (i.e., 5 years) to determine late treatment-related toxicity. It was the experience of the group that most NCI funding mechanisms for clinical research do not allow for the support required for this critical patient follow-up. Therefore, recognition of this requirement in clinical trials using radiation and providing funding for these protracted, but necessary, activities is in order.

Access to novel anti-cancer therapeutics is critical to the

development of rational combinations involving these agents and radiation. Moreover, Phase I studies using these agents in combination with radiation require a unique set of data reporting instruments which are not generally required for standard, drug-only Phase I trials. To facilitate improved radiation-related clinical research and minimize the burden on investigators using novel anti-cancer therapeutics, CTEP and other organizations should enlist input from several of these young investigators to modify the report forms and criteria, to reflect the data requirements of radiation-related clinical studies.

The workshop noted that competition for NCI-sponsored grants, including development awards, could be somewhat more difficult for radiation oncology clinician-scientists, given the time required for clinical duties. With daily treatment for most patients, even clinician-scientists with a limited volume of patients need to be accessible for patient problems. Unfortunately, there are many well-trained physician-scientists who are lost to research careers. The NCI is attempting to address such issues with newer types of grants. The group felt that it would be helpful if the Radiation Research Program of the NCI could provide specific details of funding mechanisms for radiation-related grants funded by the NIH. In addition, the group felt that ASTRO and/or the NCI could provide periodic updates to interested members regarding funding opportunities. These include requests for applications (RFA) and results on drug-radiation interaction from the proposed Radiation Modifier Evaluation program as a component of the Division of Cancer Treatment and Diagnosis, Developmental Therapeutics Program. Finally, the workshop members felt that the ASTRO membership in general, and young investigators specifically, would benefit by having these periodic updates of funding opportunities at each ASTRO meeting.

Educational barriers

Education is meant to infer information transfer about what we as young radiation oncologist/biologist/clinical investigators offer our colleagues in radiation oncology. We believe our collective research activities are vital to the oncologic and scientific community as a whole, as well as our own specialty. Without significant proactive education of residents and practicing physicians, the basic science knowledge base of our profession will be diminished, resulting in loss of control, as well as a decrement in the pool of individuals willing to pursue a research career. Therefore, we would recommend more aggressive training of residents in basic and translational research, with enhanced opportunities for their involvement in research. The recent changes in the ACR requirements make it nearly impossible for residents to have a productive laboratory experience or even follow through on a clinical project. This is clearly not adequate and needs to be addressed. The recertification of practicing radiation oncologists needs to include basic biologic concepts and requires frequent updating. A yearly review given by experts who can emphasize the clinical aspects of the new biological topics would be beneficial and

might be held at ASTRO. ASTRO can assist in this process and enhance the profile of biologic research through a greater emphasis on basic science topics at its annual meeting. The sessions are sparsely attended, and the material presented can, at times, be somewhat dated. The presentation of novel laboratory work is frequently inhibited by unnecessarily rigid time lines for abstract submissions.

Modification of the ASTRO abstract deadline would increase the available pool of presentable data. The workshop also believes the incorporation of a "late breaking" session would provide an opportunity for exciting data, not initially available for presentation at the time of the routine abstract deadline, to be presented in an unopposed scientific session. This concept works well at the AACR and ASCO meetings. We believe incorporation of these ideas and others will enhance the overall opportunities for all investigators, including young investigators. Adoption of this proactive stance also reinforces the idea that ignorance of new biologic findings/methods/techniques may be one of the most serious threats to the long-term health of our specialty.

It is also important for members of our specialty to understand that research success is intimately linked to an environment that is able to guide and nurture the young investigator and provide inspiration of ideas and critical evaluation of results. Institutions with such an environment frequently also have a track record of research excellence, as determined by numbers of grants, alumni, impact of publications, etc. Certain institutions have the capacity to provide such an environment more readily than others and could be identified as "Centers of Research Excellence." To facilitate this concept, training grants could be given priority to these "Centers," thereby providing an opportunity for individuals interested in a research career the opportunity to readily identify these centers, train at one of them, establish collaborative relationships, and identify mentors. Some precedent for this type of identification has been set; imaging "Centers of Excellence" have been identified by the NCI, providing for significant funding for the development of innovative diagnostic technologies at these institutions at levels not available at other institutions without this appellation. This approach may serve the long-term interests of both the individual researcher and the specialty as a whole by providing a conduit of well-trained faculty for continued radiation-related research into the future.

Several institutions sponsor funded, "clinical-scientist" training programs, which are particularly attractive for those interested in clinical research. Unfortunately, those individuals most interested in this career track rarely know of the existence of these programs, much less the institutions at which the programs are available. Exposure of trainees early in their career to these opportunities and establishing contact with those programs will serve to recruit and retain talented radiation oncology researchers, as well as to provide the aforementioned training environment so critical to long-term success.

It is apparent that shrinking clinical revenues are placing particularly difficult fiscal demands on radiation oncology

departments, thereby requiring more clinical work to maintain a stable revenue stream. These clinical demands are frequently at odds with the extraordinary time and effort required to establish and maintain an active, productive research career. These financial demands also tend to de-emphasize the importance of basic, translational, and clinical research particularly crucial to the long-term viability of our specialty and, more importantly, to the health and well-being of our patients. There are no easy solutions to these issues, yet constant vigilance is necessary if we are to encourage cutting-edge research to be performed and to entice new investigators into our field. We recognize that we all must work harder to reaffirm our unique role in oncologic research and therapy, crusade for more appropriate funding opportunities for radiation-related science, and identify those barriers to success which, with creative thinking, can be eliminated.

OPPORTUNITIES FOR RADIATION ONCOLOGISTS' RESEARCH

Figure 3 includes potential areas of research available to radiation oncology physicians. It emphasizes the need for continuity of research including a wide range of technical, scientific, and clinical disciplines. Physician-scientists are essential to optimize the interaction among scientific and technical disciplines and insure rapid and effective delivery of new advances to patients. Such continuity requires support of the entire specialty, including trainees, academicians, and practitioners.

NAVIGATING THE NIH GRANT SYSTEM

There is no simple way to tabulate all of the NIH grant mechanisms. Detailed information is available from the NCI home page at <http://www.nci.nih.gov/scienceresources/index.html>. Figure 4 can serve as a guideline for grants available at various phases of a career.

IMPLEMENTATION RECOMMENDATIONS

Grants

- The NCI help provide a pathway to understanding the NCI granting system. Some information is in Fig. 4. Assistance can be obtained by calling the Radiation Research Program. The RRP homepage is <http://www.nci.nih.gov/trp/>.
- ASTRO should consider sponsoring grant-writing workshops.

Mentoring

- NCI to work with ASTRO to help advise/develop collaborative mechanisms to enhance the career opportunity of early-career physician-scientists. Such support might include current NCI programs, new and current ASTRO

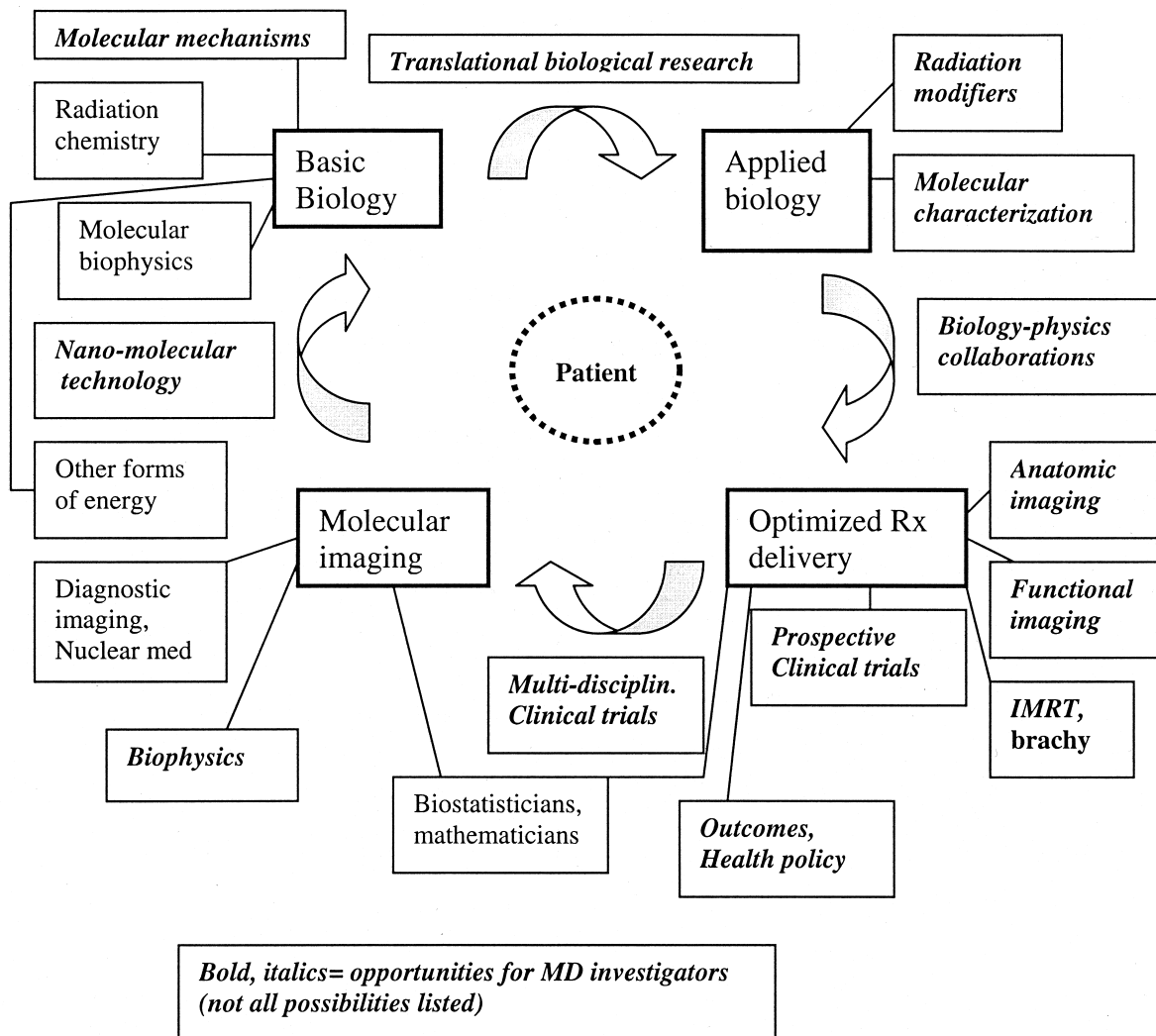


Fig. 3. Potential opportunities for radiation oncologists' research. The continuity between basic biology, applied biology, treatment optimization, and imaging is readily seen. There are many potential opportunities for research. Indeed, there are many opportunities that can only be filled by radiation oncologists. To have gaps in the availability of radiation oncology physician-scientists will compromise the ability of radiation oncology to optimize the efficacy of what our discipline can contribute to cancer care in the emerging molecular era. It is a responsibility of our specialty to train, sustain, and support all aspects of research. This will require partnerships among individuals from a range of scientific, clinical, and technical disciplines, universities and industry, government, and practitioners. The areas that seem most amenable to radiation oncology physician-scientists are in bold and italics; however, some of the other areas and fields not listed are certainly viable possibilities. This figure is intended to highlight the concept of continuity for continued progress.

programs, and commitments by the individual departments, universities, and hospitals.

- NCI and RRP to make a concerted effort include Young Investigators in various workshops and programs.
- The leadership of SCAROP, Residency Program Directors, and ASTRO are encouraged to address the issues of time and resources needed to train researchers and to help develop and sustain their careers, as outlined previously.

Translational research projects

- Tissue banking: NCI to look into tissue banking opportunities. (Information about access to tissue is available from the

Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis [at <http://www-cdp.ims.nih.gov/>]).

- Late effects: based on this and other workshops, RRP recognizes that there may be difficulty in obtaining funding for radiation oncology late effects studies due to the extended time period in which these may occur. A recent RRP Late Effects Workshop (September 1–2, 2000) raised similar issues.

Cooperative clinical trials

- Departments and cooperative groups will increase participation of young investigators in the cooperative

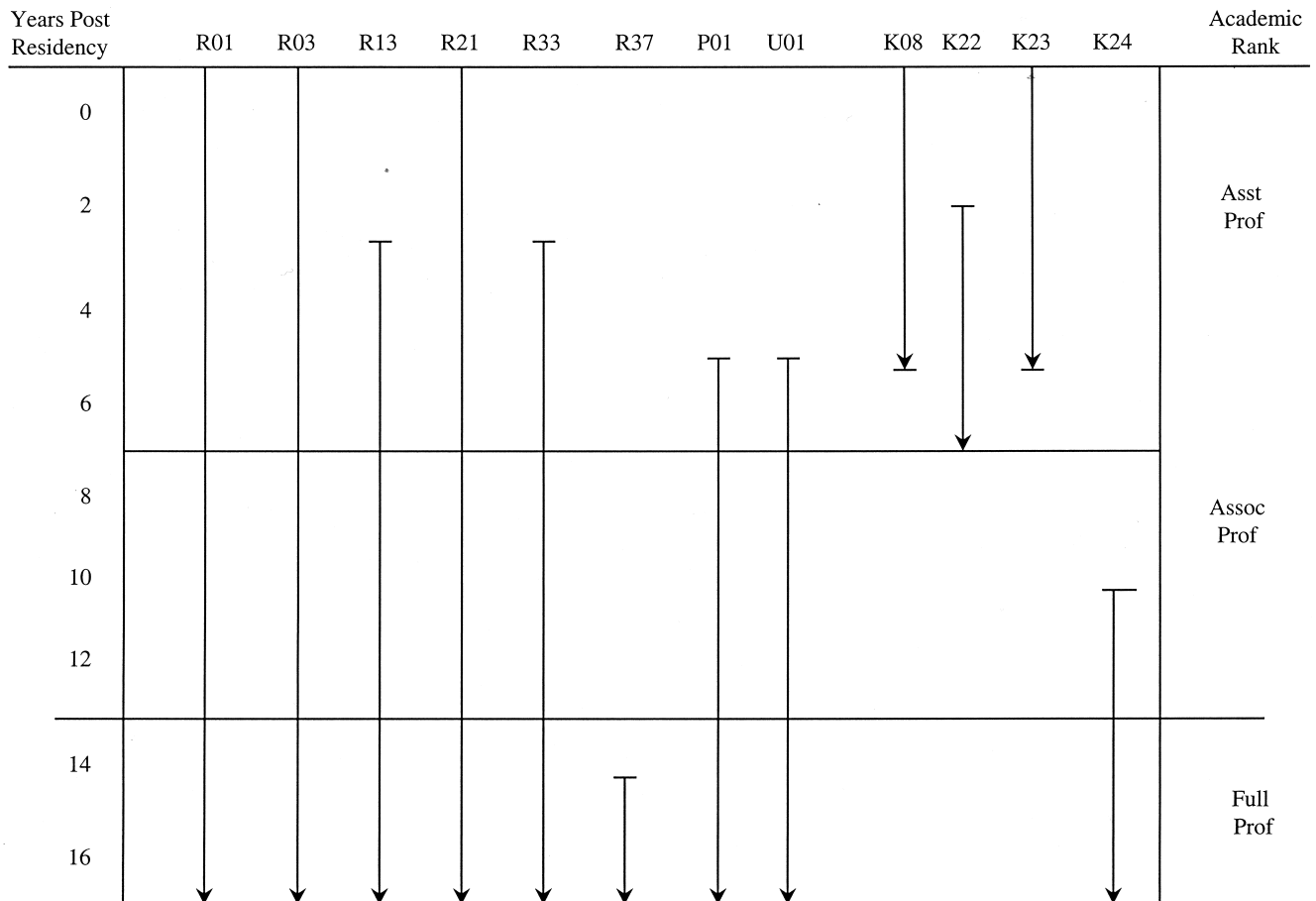


Fig. 4. Grant flow diagram. There is a wide range of grants available from NIH. A useful website is <http://www.cancer.gov/scienceresources/grantfunding.html>. This figure lists the more common grants and the likely time within an academic career that these might be utilized. R-series (research projects): R01—Research Project; R03—Small Research Grants; R13—Conferences; R21—Exploratory/Developmental Grants, R33—Exploratory/Developmental Grants Phase II (these are submitted in response to a Request for Application (RFA)); R37—Method to Extend Time in Research Award (MERIT); not listed are: R41-42—Small Business Technology Transfer (STTR) and R43-44—Small Business Innovation Research (SBIR). P-series (research program projects and centers): P01—Research Program Projects; not listed are: P20—Exploratory Grants; P50—Specialized Center. U-series (Cooperative agreements): U01—Research Project (Cooperative Agreements); not listed are: U10—Cooperative Clinical Research; U41-44 (Small Business grants similar to R41-44). K-series: K08—Clinical Investigator Award; K22—Physician Scientist Award; K23—Mentored Patient-Oriented Research Career Development Award; K24—Mid-Career Investigator Award in Patient-Oriented Research. Please see the Website for further details, or contact members of the Radiation Research Program. (Figure prepared by R. Cumberlin.)

group clinical trials that involve radiation therapy. This includes not only the continued participation in RTOG, but also involvement in the other cooperative groups.

- The RRP, in conjunction with Cancer Trials Evaluation Program (CTEP) within the Division of Cancer Treatment and Diagnosis (DCTD), will continue efforts on standard-

ization of terminology for radiation therapy and quality assurance of radiation treatments.

Centers of excellence

- The RRP will consider the concept of Radiation Oncology Centers of Excellence in conjunction with other “centers” grants supported by NIH.