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The Radiation Stress Response: Of the People, By the People and For the People

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Abstract

The radiation stress response can have broad impact. In this Failla Award presentation it is discussed in three components using terms relevant to the current political season as to how the radiation stress response can be applied to the benefit for cancer care and as service to society. *Of the people* refers to the impact of radiation on cells, tissues and patients. The paradigm our laboratory uses is radiation as a drug, called “focused biology”, and physics as “nano-IMRT” because at the nanometer level physics and biology merge. *By the people* refers to how the general population often reacts to the word “radiation” and how the Radiation Research Society can better enable society to deal with the current realities of radiation in our lives. *For the people* refers to the potential for radiation oncology and radiation sciences to improve the lives of millions of people globally who are now beyond benefits of cancer treatment and research.

Introduction

The Failla Award is given in memory of Dr. Gioacchino Failla a founding member of the Radiation Research Society (RRS), which began in 1954 (1). Starting two years after his untimely death in 1961 at the age of 70, this award was presented annually to a RRS member in recognition of a history of significant contributions to radiation research. Review of Dr. Gioacchino Failla's contributions (1, 2) included a photograph of the “Most Famous Cancer Researchers in the World in 1937”. He was a biophysicist who was working at the Cancer Memorial Hospital of New York City. He was particularly noted for his work on the role of radiation as a cause of cancer and genetic mutation. Included in the picture is radiation oncologist Henri Coutard who was chief of the department of X-ray therapy for cancer at the Radium Institute, University of Paris. As noted, Coutard ventured to extend the daily irradiation of patients to periods of several weeks (2). What is particular interesting is that 80 years later two of the key areas of radiation research are still radiation carcinogenesis and the appropriate fractionation scheme – the daily dose and number of treatments – to be used in the clinic. Scientific and technological advances allow us to address long-standing questions, often based on completely new paradigms.

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The theme of the 2016 RRS meeting of “Change the World” is used in this paper to address current and future contributions of radiation oncology and radiation sciences that can be accomplished by understanding and addressing problems important to science and society. An interesting component of the Failla Award lectures is seeing how a career has unfolded and evolved. While the focus of this presentation is on the future it will be developed in a “timeline” approach with themes interwoven over the approximately 50 years of my research career that began as a college student working in a clinical pathology laboratory of Dr. S. Raymond Gambino in Englewood Hospital in NJ (he later moved to Columbia University) and next to original research for my MD thesis on the biochemistry and diagnosis of lead poisoning in the laboratory of Dr. Howard Pearson, Department of Pediatrics at Yale Medical School. The aim of my laboratory research is to investigate problems and develop interventions directly related to improved clinical cancer care. This is now referred to “translational research”.

One's career spans a range of topics and this presentation was designed to trace the path to the current applications of the radiation stress response, as described in the abstract. Selected references mostly from the work in which I was involved are used as it is not the purpose of this paper to provide a general review. Not included are areas in which I have conducted clinical research that stimulated laboratory investigation including the description of secondary malignancies for patients with Hodgkin's disease, treatment for adult lymphoblastic lymphoma and other high grade lymphomas and treatment of prostate cancer including helping to develop MR guided brachytherapy. As a department chair at Harvard Medical School and senior member of the National Cancer Institute (NCI) radiation research programs, I have had the privilege to partner with and mentor many trainees and faculty. Perhaps few things are as rewarding as helping people realize that they have the ability to help solve hard problems for which they could make original contributions. From fairly extensive world travel starting in 1974–1975 I have had useful perspective on the diversity of people and cultures, the commonality of the need to help one another and the deep personal satisfaction one gets from service to others.

Career Perspective and Interwoven Themes toward the Use of “Radiation as a Drug”

During my training in the early 1970s medical oncology was just beginning as a separate subspecialty of the American Board of Internal Medicine and radiation oncology was becoming a separate specialty in the American Board of Radiology (3). Having been among the first to train and be board-certified in internal medicine, medical oncology and radiation oncology, and among the early researchers in clinical pharmacology of antineoplastic agents as a Clinical Associate in the Medicine Branch (Dr. Vince Devita and team) and in the Laboratory of Chemical Pharmacology at the National Cancer Institute under Dr. Bruce Chabner, my cancer research interests began in drug development. Following the training in medical oncology at NCI (1972–1974) and radiation oncology at Stanford (1975–1978), I had a dual appointment in radiology and medicine at Stanford Medical School (1978–1985), including being a co-attending in a weekly medical oncology clinic with Dr. Charlotte Jacobs in the Division of Medical Oncology led by Dr. Saul Rosenberg and also an attending in the Division of Radiation Oncology within the Department of Radiology led by Dr. Malcolm Bagshaw. My laboratory research was within the Division of Radiation

Biology (Director Dr. Robert Kalman) where I worked in Dr. Martin Brown's laboratory. In addition to working with world renowned faculty at Stanford, I was personally fortunate to have Dr. Henry Kaplan as a mentor with whom I worked on treatment related cancers in patients with Hodgkin's disease and who helped support my laboratory start-up. I am privileged to remain a friend of his family including Leah Kaplan (2004), Paul Kaplan and Ann and Bob Spears.

The composite career timeline for the perspective of this presentation is shown Fig. 1. The interwoven themes illustrate how areas of research progress and also how the focus has been on addressing problems that directly relate to patient care. This includes clinical and laboratory research and also public health and health policy, the latter related to addressing disparities in cancer care in the U.S. and globally and in health and medical preparedness for the threat of radiological and nuclear terrorism that began 15 years ago. There are three blocks of time: 1972–1985, NCI and Stanford; 1985–1999, Harvard Medical School; and 1999– to present, National Cancer Institute with 2004–to present addressing societal issues.

The Radiation Stress Response

Of the people refers to the impact of radiation on cells, tissues and patients. The paradigm our laboratory uses is radiation as a drug called “focused biology” (4, 5) in that the dose size, fractionation and type of radiation will produce different changes. We consider physics as “nano-IMRT” in that physics produces biological changes which we believe is a preferable understanding of its impact on cancer care rather than just the use of dose in Gray.

Pharmacology Perspective of Anticancer Agents and Drugs that Address Tumor Hypoxia

Clinical pharmacology of antineoplastic agents was in its infancy when I began my post-doctoral training. Four of us in the NCI pharmacology laboratory co-authored one of the earliest reviews on this subject (6, 7). My specific project involved understanding the metabolic activation and inactivation of cytosine arabinoside via deoxycytidine kinase (8) and cytosine deaminase, respectively, (9) to determine which patients may respond. This is a biomarker similar in concept to today's precision medicine. We discovered that the kinase/deaminase ratio was substantially higher (greater activation) in the immature cell population from normal marrow and from the circulating blood of patients with acute myelogenous and chronic myelogenous leukemias (8). This is a subpopulation enriched in stem cells, another key concept of today's precision medicine.

The importance of the tumor microenvironment on treatment response had been recognized by radiation biologists since the 1950s and attempts to overcome hypoxia-related radioresistance included the use of multi-fraction radiation therapy (reoxygenation), hyperbaric oxygen and oxygen-mimetic radiation sensitizers (10). As a clinician-pharmacologist, I had the opportunity to join the exciting laboratory of Martin Brown and colleagues at Stanford who were developing nitro-imidazole compounds that would avoid the neurotoxicity of misonidazole. The less lipophilic compound etanidazole (or SR-2508) was developed and tested in clinical trials (11). While about three times the amount of drug could be delivered compared to misonidazole validating the approach taken by Brown *et al.*, it still produced neurotoxicity; however, having a team with expertise in radiation biology

and in clinical pharmacology it was possible to use pharmacokinetics and pharmacodynamics (PK/PD) to reduce the risk of neurotoxicity (12, 13). By measuring the single dose area-under-the-curve (AUC) of plasma concentration versus time, it was possible to greatly reduce the risk of toxicity from ~60% to 6% by prescribing for a total AUC for each patient rather than dosing by body surface area. This avoided both under-dosing and toxicity. Indeed, this may have been the first cancer drug that was dosed by PK/PD. While it never entered clinical trials, an oral prodrug of etanidazole had been developed in my project based on PK/PD principles (14).

Clinical trials with etanidazole were null, felt to be due to the inability to give a high enough dose for enough of the treatments. There is a resurgence in interest for use of etanidazole or related compounds with hypofractionated radiotherapy (15). That the concept of tumor hypoxia is relevant in the clinic has been demonstrated by Overgaard (16) in his outstanding work with nimorazole. There is now a great deal of work on the broader molecular impact of hypoxia and recent biomarker work on signatures to predict which tumors may respond to treatments that address hypoxia (17). With my perspective of drug development and radiation biology, I proposed the concept of hypoxia as a paradigm for biochemical and physiological heterogeneity in tumors (18). Over the last 15 years the application of newer research techniques has greatly enhanced the knowledge of hypoxia biology and the stress response, some of which I was involved in (hypoxia inducible factor, HIF) when studying the mechanisms of non-steroidal anti-inflammatory agents (NSAIDs) (19) as radiation modifiers, discussed below.

The clinical focus for addressing tumor hypoxia led by Brown and others progressed to the development of drugs that selectively kill hypoxic cells rather than sensitize them to radiation. Tirapazamine was the drug initially developed for clinical use (20). In the transition from Stanford to Harvard, our research team worked in the initial phase I clinical development of tirapazamine with my medical oncology colleague, Dr. Larry Shulman (21). This included describing the major toxicity of muscle cramping (22) along with colleagues with expertise in free radical biology from University of Pennsylvania and NCI investigating mechanisms of toxicity (23). Working with colleagues at Harvard we also studied potential uses of tirapazamine with drugs and/or hyperthermia (24, 25). The use of hypoxic cytotoxic agents remains an active area of preclinical and clinical investigation with evofosfamide (TH-302) by other groups.

The Molecular Biology Era and New Approaches

With the transition to Harvard and a new laboratory group, we developed a focus different from the Stanford lab. This transition was easy with the spectacular revolution in genetics including the early understanding of oncogenes and tumor suppressor genes and with molecular biology techniques allowing for a greater level of sophistication in the development of new paradigms including radiation biology. Our lab explored radiation-induced apoptosis, when this process was just being described (26, 27) and survival pathways such as NF- κ B (28). The next major change in direction resulted from a clinical observation from a single patient that I was treating for prostate cancer. He was having fairly severe acute toxicity with urinary frequency and burning, not due to infection. The NSAIDs

[cyclooxygenase (COX) inhibitors] were relatively new and I prescribed a fairly high dose of ibuprofen, being concerned about the gastrointestinal bleeding. He was remarkably better after the first few doses, prompting us to consider the use of the NSAIDs that modified prostaglandin metabolism to reduce toxicity. It was not lost on us that prostaglandins were first described in the prostate gland. Before embarking on the use of ibuprofen to reduce clinical toxicity it was first necessary to be sure that the drug did not protect against tumor cell killing by radiation.

The preclinical study *in vitro* and *in vivo* demonstrated that ibuprofen was a radiation sensitizer (29) and did not protect the tumor. The phase III symptom-relief trial of ibuprofen for prostate radiotherapy was negative, possibly due to the limitations in the scales that assess toxicity (30). Seeing all the promising data in the literature on the many mechanisms of the COX inhibitors as anti-cancer agents we recognized the need to study both the cyclooxygenase effects (on-target) and non-cyclooxygenase (off-target) effects of the NSAIDs. Among the links between the NSAIDs and our interest in hypoxia was the impact of ibuprofen on reducing the hypoxia inducible factors HIF-1 α and HIF-2 α (31). After we demonstrated that siRNA against COX-2 reduced the protein but did not affect radiosensitization (32) we realized it is critical to consider the effects of the clinically relevant drug concentration before proceeding with the clinical trial we had written but not activated for patients with locally advanced prostate cancer.

The Importance of Clinically Relevant PK/PD

In preparation for the clinical trial we needed both a realistic assessment of potential benefit for the patients and also a biomarker of drug effect. Others were conducting clinical trials based on preclinical laboratory data but we did not proceed. We were fortunate to be working at the NCI with Dr. Ed Liu, the Director of Clinical Sciences who established the Advanced Technology Center which provided the opportunity to access relatively low-cost microarrays. We worked with collaborators in the Radiation Biology Branch, Dr. Jim Mitchell, Branch Chief and Dr. Eric Chuang (now at National Taiwan University). Using the relatively high and also the clinically relevant concentrations of the nonspecific COX inhibitor (ibuprofen), a COX-2 specific inhibitor (NS398) and siRNA for COX-2 in PC3 prostate cancer cells and also in coronary artery smooth muscle cells and endothelial cells we demonstrated the major difference in gene expression between the high and clinically relevant concentrations and also that siRNA produced a different pattern than any of the other drug groups (33, 34) (Fig. 2). The issue of the lack of reproducibility and predictability of preclinical data for clinical trials had not yet arisen (35) but has since been a focus of much attention. Recognizing the need to fully understand the impact of clinically relevant drug schedules we realized that there was a gap in the knowledge of the impact of clinically relevant multi-fraction radiation.

Clinically Relevant Radiation: What Actually Happens and (How) Can One Use Radiation as a Drug?

The next experiment was done in collaboration with Tsai and others from the Radiation Biology Branch (36). We postulated that cells that survive fractionated radiation might induce a survival pathway, as indicated by gene expression pattern, that makes them

susceptible to killing by a drug. This was along the lines of synthetic lethality as described by Kaelin (37) in which a tumor by virtue of a mutation in one survival pathway is susceptible to killing by inhibiting an essential compensatory or alternate survival pathway (38). We postulated that a radiation-induced pathway might take the role of the mutated pathway in the synthetic lethality concept and thereby allow for tumor cell killing by inhibiting of the compensatory or alternate pathway, as occurs with a PARP-inhibitor in the presence of a BRCA mutation (38). Tsai used three cell lines and tumors, breast (MCF7), brain (SF539) and prostate (DU145), with radiation of single dose (SD) 10 Gy $\times$ 1 and multi-fraction (MF) 2 Gy $\times$ 5 *in vitro* and *in vivo* (for DU145) and examined gene expression at 0–24 h postirradiation. He demonstrated that more genes were turned on and were on more stably after MF compared to SD. Of interest, and particularly relevant to the current interest in immune modulation, were the upregulation of interferon and TGF- β /SMAD-associated genes more so after MF than SD. There were differences between *in vitro* and *in vivo* (36). We recognized that studying the reality of what happens to cells exposed to clinically relevant radiation schedule might produce a new paradigm for radiation in our “focused biology” concept. In that our laboratory had experience with prostate cancer and radiation is frequently used often as a single modality, we proceeded to study prostate cancer as our initial model system with the following hypotheses tested and translational questions:

1. Cells that survive fractionated radiation may have an altered phenotype that is potentially more susceptible to drug therapy.
2. The fractionation regimen may be chosen to optimize induction of specified pathways.
3. By using this approach, it may be possible to expand the scope of radiation therapy for use as a molecular targeted therapy.

A model of how this might work is shown in Fig. 3, adapted from Luo (39). The evolution of the thinking of the hallmarks of cancer went from oncogene addiction in 2000 to include nononcogene addiction in 2009. Conceivably, radiation can modulate the stress responses and evasion of immune surveillance and make tumors targetable. Figure 4 includes the experimental design and model systems currently under investigation in our laboratory. The *in vitro* systems and the PC3 prostate *in vivo* experiments are done in our laboratory; PC3 immunotherapy studies are done in collaboration with Dr. Jim Hodge in Laboratory of Tumor Immunology and Biology, NCI (40); and the TSA mammary carcinoma studies are conducted by collaborators Drs. Sandra Demaria and Sylvia Formenti (41) of Cornell University. Some of the key findings include:

- Gene expression is substantially different after SD and MF. Figure 5 includes the data from Tsai (36), mentioned above, and from Aryanakalayil (42) for miRNA. Similar patterns are seen for mRNA (43). In the prostate miRNA data, it can be seen that MF of 0.5 Gy $\times$ 10, a schedule that had ~85% cell survival, produced substantial changes. Details of the gene ontology and pathway analysis are in the individual papers, referenced here. Among the key pathways upregulated are those of immune response.

- Using 1 Gy fractions twice a day or thrice per day, there is an inflection point in gene expression after 6–8 fractions as shown in Fig. 6 (43, 44). That it takes a number of “hits” to begin to change phenotype, at least by RNA analysis, may be relevant to multi-fraction regimens often reported *in vitro* that are usually only a few in number ($n=3-5$) so that they may miss this inflection point. Also, that the changes can occur in only a few days makes this potentially quite relevant to a course of combined modality therapy with radiation plus drugs or immunotherapy. Notably, we are examining other changes such as metabolomics that may produce a different inflection point and different targetable changes.
- The gene expression of a baseline microarray does not predict its response to SD or MF (42). In that in current clinical care an initial tumor profile is often used to determine a course of treatment for a patient, it may be appropriate to re-interrogate the tumor relatively soon after the initial treatment to tailor the treatment to the adaptation. This might require a number of mid-course changes. In molecular-targeted drug studies, tumors are often studied at the time of emergence of resistance, however, it might be advantageous to study them as they respond. The challenge will require biomarker assays, potentially including circulating nucleic acids, exosomes, etc. and also imaging.
- When using radiation to enhance immune response the dose and fraction size matters. In Fig. 7, Dewan's study with radiation and anti-CTLA-4 showed MF of 8 Gy $\times 3$ to be equally effective as SD 20 Gy for local tumor control but the MF lead to an effective abscopal effect not seen with the SD (41). A distinct difference is seen for gene expression in signal transduction and DNA repair genes for different fractionation schemes *in vivo*. Details of immune related genes are included are in a separate publication (45 in preparation) (Fig. 7). The relevance is that many of the immunomodulating clinical trials are using a limited number of high dose fractions and that a larger breadth of dose and fractionation should be considered. The NRG cooperative group is conducting a trial using a priming MF dose of 0.5 Gy.
- That the expression profile differs after MF and SD is seen also seen in human endothelial and smooth muscle cells (44). Given the multiple fields used in clinical radiation therapy a substantial amount of normal tissue will see some repetitive dose in this range that could influence both immune and normal tissue response (5). The initial tumor genotype matters as seen for LNCaP cells with normal p53 compared to PC3 with p53 deleted and DU145 with p53 mutated (46).
- Having demonstrated that both SD and MF impact immune response and abscopal effect differently working with collaborators, our laboratory is focusing on the induction of druggable molecular pathways. Eke has demonstrated for DU145 cells in 3-dimensional tissue culture that MF can induce the mTOR-AKT survival pathway and that drug inhibition resulting in cell killing occurs after MF but not before (47 in preparation). Taking advantage of radiation-induced

susceptibility will likely require multiple druggable targets, possibly including proteomic, metabolomics and epi-genetic changes.

- The future clinical use of the paradigm of radiation-inducible molecular targets is a work-in-progress for use with drugs (48, 49) and immunotherapy (50). It should also be considered for other forms of radiation, particularly particle therapy as that has advantages of physical localization and biological changes (51, 52).

How radiation can best be used as a drug in addition to its long-standing use for cell killing by itself remains to be further developed. That there are clear limits to the curative efficacy of any single molecular targeted drug is apparent due to tumor heterogeneity and evolution for which much has been written, Jamal-Hanjani providing a recent example (53). While we are in an exciting new era of precision medicine with drugs, the limits are becoming more apparent (54) so that novel approaches using radiation are certainly warranted. To bring together this component of the radiation stress response two concepts are presented regarding radiation dose and fractionation:

- *Shades of Gray*: The unit of radiation dose, the Gray (Gy), is critical for calibration of machines but tissues experience the radiation differently for photons, fractionation, hadrons and systemic radionuclides. It might be better to also consider dose in biologic terms such as lesions produced, pathways activated and other changes.
- *Tumor Annoying Dose, or TAD of Radiation*: Tumor cell killing by radiation is a key goal and it is very effective in many circumstances. However, there are times when radiation may be used to stimulate susceptibility to other treatments as with an immune priming dose or with radiation-inducible molecular targets. Given the inflection point in MF adaptation, the radiation dose and fractionation may be varied during a course of treatment to produce a distinct targetable biological effect.

The Radiation Stress Response

By the people refers to how people react to the word “radiation” and how the RRS can better enable society to deal with the current realities. The general issues of environmental and medical radiation risk are certainly critical areas of research and investment for radiation research. This section focuses on the role of radiation science experts regarding the threat of intentional radiation exposure that resulted from the terrorist attacks on September 11, 2001 and the risk of catastrophic exposure encountered during the Japan nuclear power plant crisis in March 2011.

Following the terrorist attacks in 2001 a workshop was held in Washington, DC (55) that defined the moderate dose-range (1–10 Gy) generally single whole body exposure as the one to focus on for the development of post-exposure medical countermeasures. Dr. Paul Okunieff was instrumental in stimulating this meeting. The moderate dose descriptor distinguished this from the low-dose region in the environment and from the higher clinical doses given during radiation therapy. New research programs, distinct from those supported

by NCI, were initiated through the Radiation and Medical Countermeasures program in the National Institute of Allergy and Infectious Diseases (56) and advanced development programs by the Division of Chemical, Biological, Radiological and Nuclear Medical Countermeasures within the Biomedical Advanced Research and Development Authority (BARDA) as part of the Pandemic All-Hazards Preparedness Act (PAHPA) (57). These continue to provide opportunities for research and development and complement those from NIH. The potential shortage of expertise in radiation biology was noted soon after we proposed new research and development programs (58). This is a serious ongoing issue being raised by the National Council on Radiation Protection and Measurements (59).

In addition to the need for laboratory research, there are critical roles and opportunities for radiation scientists in policy and health and medical disaster preparedness. A recent report *Public Health and Medical Preparedness for a Nuclear Detonation: The Nuclear Incident Medical Enterprise* (60) summarized over 12 years of efforts in this important field and a few points of opportunity for radiation scientists will be emphasized.

The approach to nuclear disasters differs from prior research on radiation protection in that the medical countermeasures would be given post-exposure not pre-exposure, since these would be no-notice incidents. Thus, the term radiation “mitigators” is used for this setting to contrast pre-exposure “protectors”. In that the acute exposure, might lead to complications weeks or a few months later, the term “delayed effects of acute radiation exposure, DEARE” was introduced to fill the gap between acute, immediate effects and delayed, late effects that may occur many months or years later. The need for diagnostics to help guide medical experts in triage and treatment decision, particularly critical in a scarce-resources setting, became apparent. An example of the need for scientific expertise to determine policy is work performed by Sullivan (61) who reviewed the details of each of the biomarker assays and provided guidance on when each could produce clinical results and within what dose range. Figure 8 indicates the importance of diagnostics in the serial triage, with stars showing key roles for radiation science in the point-of-care and high throughput diagnostics and also in developing medical countermeasures including guidance for their optimal use.

Figure 9 illustrates the Nuclear Incident Medical Enterprise (NIME) (60) that has been developed since September 2001 with the potential role for radiation experts for science, preparedness and policy. The primary references for each of these components are in the NIME paper (60). A key aspect is the need for science underpinning of policy and implementation plans, designated by the arrows, red for concepts and green for implementation in preparation for and use during a response.

That preparedness is essential for response and resilience was demonstrated in the response for the Fukushima nuclear power plant crisis. By virtue of having experts in nuclear issues on site working with U.S. ambassador John Roos in Tokyo and seeing what processes could be improved a multi-agency group developed a new concept called “the medical decision model” (62, 63). Additionally, despite the enormity of the disaster in terms of lives lost and disrupted and physical infrastructure destroyed, an overwhelming global fear was exposure to radiation and the potential for radiation-induced carcinogenesis (64). In response to this,

there is ongoing interest to consider the potential to develop strategies and agents for post-exposure mitigation of radiation-induced cancer (65).

How this aspect of the radiation-stress response relates to daily cancer care can be seen in three ways: (1) Radiation biodosimetry includes studying molecular and biological changes that indicate organ injury so these might serve as clinical biomarkers of tissue injury and response. (2) With more radiation therapy now given by a single dose or a few large doses, the use of mitigators developed for a nuclear/ radiological incident might be useful for post-exposure use in clinical care. (3) That society both needs and appreciates input and contributions from scientists was seen in the role scientists and radiation experts played in the response to the Fukushima crisis (66).² These needs and opportunities broaden the potential career paths for scientists including the opportunity to work on projects in government and academia that benefit from the ability of scientists to take on hard problems not yet solved and move effectively toward new knowledge, solutions and policy. Government has many experts in process that must be complemented by those with content knowledge. The combination is particularly effective. There are fellowships such as those by the American Association for the Advancement of Science (67) that enable scientists to experience careers in science and technology policy.

The Radiation Stress Response

For the people refers to the potential of radiation oncology and radiation sciences to improve the lives of people who are now beyond our current reach.

That radiation therapy is extraordinarily effective for cancer cure, control and palliation is well known. The International Atomic Energy Agency (IAEA), the major international agency involved in radiation matters, has programs related to both security of nuclear material (68) and cancer care, the Program for Action for Cancer Treatment (PACT) (69). The World Health Organization (70) has highlighted the importance of addressing the non-communicable diseases (NCDs) that are an increasing burden on low- and middle-income countries (LMICs) (70). These include cardiovascular, respiratory, metabolic and oncologic diseases. Infectious diseases remain important for epidemics and are also relevant to cancer, for example, with cervical, head and neck and liver cancers. Currently, approximately 70% of NCDs occur in the underserved world which have few resources. Notably, there are similar shortages in wealthy countries with geographically-isolated indigenous people. The IAEA Directory of Radiotherapy Centers (DIRAC) (71) indicates that many countries have little or no radiotherapy capacity and that overall there is currently a global shortage of at least 5,000 linear accelerators. Given the central role for radiation therapy, there is a potential role for experts in radiation therapy, technology and radiation sciences to be involved in health disparities and in global health.

That there are communities that receive inadequate cancer care in the U.S. and other resource-rich countries is a reality. While at Harvard, we created a novel model for linking academia with the community to deliver cancer care (72) and while at NCI we have established programs to reach underserved populations, an excellent example being that for

²I received the Samuel Hayman Service to America, Homeland Security Medal in 2011 for this contribution.

American Indians in South Dakota by Dr. Petereit and colleagues from the Lakota Sioux tribe (73). Over the last few years there has been a substantial increase in addressing the shortfalls in global health (74) with the rapidly rising burden of NCD's in LMICs recognized in 2011 by the United Nations General Assembly (75).

Atun and the Global Task Force for Radiation for Cancer Control did a comprehensive analysis on the gaps in access to radiation and in a seminal paper demonstrated that developing radiotherapy services is not only good for people's health but is also of positive economic benefit (76). There is tremendous interest by early career leaders (77) in a career path that includes global health (78). Potential implementation plans have been described elsewhere (79). The possibility of creating a global health corps has been demonstrated by Gupta (80). With the aim of building capacity and capability in LMICs and also for indigenous populations in upper income countries, the International Cancer Expert Corps, a nongovernment organization, has been established so that long-term sustainable mentorship relations can be established as shown in Fig. 10 (81, 82). With the goal of the ICEC Center and the Associates therein to ultimately pass a quality assurance site visit so that they could join global clinical protocols, there is the need for a wide variety of mentors. These are not limited to medical personnel (82). Being a nongovernment organization and also global from the outset ICEC can partner with other agencies such as the Center for Global Health at the NCI (83), PACT in IAEA (69) and academia. This includes the Consortium of University for Global Health (84) and the Union for International Cancer Control (85).

An unexpected but very exciting collaboration has been established among agencies interested in cancer care, agencies interested in security of nuclear material and nongovernment groups interested in stopping nuclear proliferation. Their combined focus has created a new paradigm "Treatment, not Terror" (86, 87) that emphasizes the priority of cancer treatment in the efforts to remove potentially dangerous medical nuclear material, such as cobalt-60, from poorly secured places. This has led to a workshop in Geneva in November 2016 to discuss the potential for developing a linear accelerator designed for the challenging environments in LMICs and underserved geographic locations in resource-rich countries (personal communication). The opportunities for a wide spectrum of volunteers to join ICEC, including radiation biologists, physicists, statisticians, etc., can be found on the ICEC web site (82).

Science, Service, Society and Resources

The three components of the "radiation stress response" address science, service and society. I believe it is critical to link these as they not only provide a spectrum of opportunities for radiation researchers, radiation oncology healthcare providers and radiation scientists but this approach also provides multi-dimensional opportunities to bring together various sectors of academia, government, the economy and global partnerships (88). The budgetary challenges for the support of science and research including the decline in purchasing power research dollars are well known (89). The positive aspect of this funding curve was that there are two examples of society and politicians strongly supporting science, the doubling of NIH budget and the post-recession 2009 stimulus. While science for its own sake is essential, when scientists help society with issues that concern and serve the greater good there is

public advocacy for what we do. Certainly, the politicization of so many scientific issues is apparent, yet enthusiasm is also apparent for new knowledge and “breakthroughs” and when scientists do participate in situations such as the Japan crisis, there is clear appreciation for the knowledge and skills we bring to the table or fight, as it were.

In the optimistic approach to the future (66), I proposed that the classical academic pillars of research, teaching, clinical care, mentoring and administration be expanded to include social responsibility, policy, mission and service to society. That some of the latter are not “revenue producing” is a challenge facing clinicians and scientists as it requires resource sharing in perhaps unique models (90). It is critical to have an ongoing investment in the future generations so that radiation and related sciences are able to provide the important contributions for which society, individuals and partners are dependent.

It's about People

The closing part of Failla Award lectures is often a recognition and appreciation for the help and contributions of so many people that enables one to achieve their accomplishments in work and life, both great and small. All matter. My family, who supported the idea of a healthy life style, interest in learning about the diversity of cultures in this world and taking on hard challenges were essential. Mentors, colleagues and friends were noted. They were essential to my ability to address problems of science, service and society that needed to be addressed. Two special colleagues who have passed away recently were mentioned. The Radiation Research Society and its multi-specialty membership – biology, medicine, physics and chemistry – bring us in contact with a breadth of superb colleagues. Both William Bernhard, who succeeded me as President and who became a triathlon and trekking friend, and Bill Morgan, whose humor enlivened many a meeting and who fought tirelessly for radiation research would likely have given a Failla lecture. In challenging times for science and society, as we now face, they would have reminded us of the extraordinary breadth of radiation sciences for us to undertake with frontiers to explore with endless optimism (Fig. 11). They would have recognized the approach in this talk, Fig. 12 shows that we are perhaps unique in being able to work from the very basic aspects of physics track structure, chemistry and biology, through to complex systems “of, by and for the people” (91) and have major impacts on lives of individuals and society, in addition to what we bring to cancer care. There are bright horizons with hard challenges and frustrations along the way, but there are rewards and personal satisfaction simply for taking them on. Balance in life is important which we each find in our own ways, being mindful of the needs to those around us. While length, breadth and depth certainly matter, President Lincoln provided an appropriate conclusion (92): “And in the end, it's not the years in your life that count. It's the life in your years”.

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Evolution of the Research: a timeline

FIG. 1.

Evolution of research and interwoven themes. The themes are illustrated over three major career segments, 1972–1985, Stanford and NCI; 1985–1999, Harvard; and 1999–to present, NCI including 2004–to present with the Office of Assistant Secretary for Preparedness and Response in the Department of Health and Human Services.

Preclinical work for NSAIDs for a clinical trial: Must use relevant doses for clinical mechanisms and biomarkers.

FIG. 2.

Difference in mRNA expression of tumor cells and normal tissues after exposure to both between clinically relevant concentrations and high concentrations of COX inhibitors often used in the laboratory. Prostate cancer cells were exposed to ibuprofen (nonspecific COX inhibitor), NS-398 (COX-2 inhibitor) and siRNA with concentrations noted. Changes in signal transduction pathways are shown but similar effects were seen in a wide range of gene ontology groupings. (33, 34)

Radiation as “focused biology”:

How can the radiation-induced stress response *be used to produce targetable changes?*

FIG. 3.

How radiation-induced stress response fits within the “hallmarks of cancer”. The hallmarks of cancer have expanded from oncogene addiction to include non-oncogene addiction. The stress responses and immune surveillance could potentially be modified by radiation for therapeutic advantage with combination therapy including molecular targeted therapy, immunotherapy and regular chemotherapy. [Adapted from ref. (39)]

FIG. 4.
Laboratory models for studying single dose (SD) and multifraction (MF) radiation.

Some highlights: Fractionation Matters

FIG. 5. Difference in mRNA and miRNA expression after SD and MF radiation. Difference in gene expression between SD and MF for three tumor types (left side). After MF more processes were modified for a more sustained period of time. Similar findings are seen for miRNA (right side). Notably, changes occur for MF using a dose of 0.5 Gy (42, 43).

When does MF- adaptive occur and how could it fit in combined modality treatment? # fractions > time (but both)

Inflection Point 2x vs 3x per day – around 6-8 fractions

Aryankalayil et al, Radiat Res. 2014 Aug;182(2):139-48

FIG. 6.

Inflection point after MF radiation. For the two interferon related genes shown, the change in gene expression occurs after approximately 6–8 fractions. This occurs for the MF given twice or three times per day. That the adaptation occurs rapidly, within 2–3 days, can allow this approach readily fit within combined modality therapy. Changes in other “omics” including metabolomics and proteomics are also being investigated (43, 44).

Radiation in vivo: fractionation matters

FIG. 7.

Single dose and multifraction dose produce different abscopal effects and expression of immune response pathways. Dewan *et al.* (41) have shown that while SD and MF schedules are similarly effective for treating the primary tumor, the schedule of 8 Gy × 3 is most effective for the abscopal effect. The gene expression patterns for SD and MF *in vivo* for both signal transduction and DNA repair are different. Similar data for immune response genes will be in a publication by Demaria. Therefore, using a “one-size fits all” radiation schedule for immune priming or for inducing molecular targets may miss important uses for radiation. [Differentially expressed Signal Transduction genes in at least one of 4 comparisons (>twofold, paired *t* test $P < 0.05$, 89 probes) are displayed as normalized to the 0 Gy control within each set. Differentially expressed DNA Damage Repair genes in at least one of four comparisons (>twofold, paired *t* test $P < 0.05$, 28 probes) are displayed as normalized to the 0 Gy control within each set.]

Incorporation of medical triage (T) with coordinated biodosimetry and medical countermeasure treatment

FIG. 8.

There is a need for scientists in health and medical disaster response policy and preparedness. This example is for triage and medical countermeasure use. During a large scale nuclear or radiological incident, there is the need to triage patients into treatment category. This requires scientific expertise for developing biodosimetry assays and for developing medical countermeasures for radiation injury and the indications for their use. Colored tiles are triage category; T-serial triage (61).

IND: Toward solutions Nuclear Incident Medical Enterprise (NIME)

From Coleman et al., 2015, Health Physics, 108:149-160.

ASPR: Resilient People. Healthy Communities. A Nation Prepared.

FIG. 9.

Nuclear incident management enterprise (NIME) and need for radiation scientists. Health and medical preparedness for a radiological or nuclear incident requires a broad range of expertise. Indicated are potential roles for scientists as laboratory scientists and also for expertise in establishing policy and preparing tools to aid in incident response (60).

FIG. 10. International Cancer Expert Corps, Inc. (ICEC) sustainable mentorship model. There is a growing burden of cancer in underserved communities globally. The ICEC mentorship approach is largely focused on medical care but there are opportunities for mentors with expertise in radiation biology and also for healthcare policy (82).

FIG. 11.

Breadth of radiation research within federal agencies. Radiation sciences are of importance to society in a broad range of applications, including but also well beyond cancer research.

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FIG. 12.

Scope of radiation research: of the people, by the people, for the people, a phrase from Lincoln's Gettysburg address (91). The scope of radiation impact: of the people (cell, molecular, biochemical; physiology, systems, organism, person); by the people (toxic effects, radio-phobia; mitigate injury, reduce fears); and for the people (global cancer burden and world peace; frontiers to explore, endless boundaries).