Workshop

“Radiation, Senescence, and Cancer”

National Cancer Institute, Bethesda, MD, USA

10th & 11th August 2020

Organizers

Radiation Research Program (RRP), Division of Cancer Treatment and Diagnosis (DCTD), NCI

Pataje G. Prasanna, PhD.
C. Norman Coleman, MD.

Center for Cancer Research (CCR), NCI

Deborah E. Citrin, MD.

University of Florida, Gainesville, FL

Daohong Zhou, PhD.

Scientific Planning

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Deborah E. Citrin, MD.; CCR, NCI
Daohong Zhou, PhD., University of FL
Jeffrey Hildesheim, PhD.; Tumor Biology and Microenvironment Branch, Division of Cancer Biology, NCI
Michael G. Espey, PhD.; RRP, DCTD, NCI
Sundar Venkatachalam, PhD.; Developmental Therapeutics Program, DCTD, NCI
Dan Xi, Ph.D., Office of Complementary and Alternative Medicine, DCTD, NCI
Gabriela Riscuta, MD., CNS.; Nutritional Science Research Group, Division of Cancer Prevention, NCI

And the Members of the RRP and CCR, NCI

This workshop will provide a forum for the leading investigators in radiation treatment, senescence, and cancer research fields to discuss the current status of senescence research and senolytic therapy in relation to chemoradiation. The speakers will identify the key gaps of knowledge in the discovery, development, and translation of senotherapeutics (includes both senolytics and senomorphics) for clinical use.

Cellular senescence has typically been defined as irreversible cell growth arrest and is an essential tumor-suppressive mechanism that prevents the propagation of genetically unstable and damaged cells and promotes their removal by the immune system. Induction of cancer cell senescence is also one of the essential underlying mechanisms by which radiation and chemotherapy exert their anti-tumor activity as they can activate not only many cell-signaling, proapoptotic, pro-survival, and tumorigenic molecular pathways, but also cause premature senescence; a striking intersection that may be shared and pivotal in controlling and regulating cancer and senescence. However, immune suppression induced by radiation and chemotherapy can lead to rapid accumulation of senescent cells (SnCs). A growing body of evidence demonstrates that SnCs can promote tumor growth, relapse, metastasis, and resistance to therapy, in part via secretion of a plethora of inflammatory mediators (e.g., cytokines and chemokines), growth factors, and extracellular proteases – termed the senescence-associated secretory phenotype (SASP).

Furthermore, malignant cells can acquire stemness upon therapy-induced cellular senescence and become self-renewing tumor-initiating cells to cause tumor relapse and drive a much more aggressive growth phenotype. Moreover, through the expression of SASP, SnCs can also contribute to radiation and chemotherapy-induced side effects, such as tissue fibrosis, bone marrow suppression, cardiovascular, and renal dysfunction. These findings suggest that cellular senescence is a double-edged sword in the fight against cancer with radiation and chemotherapy. Inhibiting senescence induction can be damaging but promoting SnC clearance after radiation and chemotherapy could be potentially beneficial. This view is supported by several recent studies, which show that a novel “double punch” cancer therapeutic approach consisting of a therapeutic strategy to induce senescence in tumor cells and followed by selective clearance of SnCs with a senolytic agent could be a more effective treatment for many different cancers. In addition, agents that suppress SASP (that drives aging) using senomorphics can also reduce and mitigate a variety of side-effects of treatment.

There are many outstanding questions that need to be addressed before senotherapeutic approaches can be used to treat cancer patients in the clinic. Could radiation/chemotherapy be used as a model to induce and study cellular perturbations that cause senescence and/or caner? What are the differences in treatment induced senescence in normal tissue and tumor microenvironment? Can it be used to unravel the intersecting mechanisms of tumorigenesis and senescence? Will this be a viable approach to discover and develop novel senotherapies that can also serve as novel cancer therapies? Can senotherapeutics improve the efficacy of radiation and chemotherapy without compromising anti-tumor immunity? Is the timing of senotherapeutics following radiation and chemotherapy important for determining the therapeutic efficacy of the “one-two punch” cancer therapeutic approach? Are there any biomarkers that can be used to monitor the effectiveness of senotherapeutics?

Agenda

Day 1: August 10, 2020

9:15 – 9:40 AM	***Virtual Arrival***
9:40 - 9:50 9:50 - 10:00	Logistics, Background, and Charge for the Meeting: Pataje G Prasanna, NCI Welcome and Introduction of the Keynote Speaker: C. Norman Coleman, NCI
10:00 – 10:35	**Keynote** Protecting the bone marrow from ionizing radiation; Norman E Sharpless, Director, NCI.
Session I: Hallmarks of Cellular Senescence and Cancer *Moderators: Jeffrey Hildesheim, NCI, and Jan van Deursen, Rochester, MN*	
10:40 - 10:55	Senescent cells as both drivers and suppressors of radiation-induced cancers; *Judith Campisi, Buck Institute, Novato, CA*
10:55 - 11:10	Animals models to study the role of senescence cells in diseases and cancer; Jan van Deursen, *Rochester, MN*
11:10 – 11:25	Radiation, senescence, and diseases: Stephen Brown; *Henry Ford Health Systems, Detroit, MI*
11:25 -11:40	Senolytic and senomorphic therapy; Laura Niedernhofer, *University of Minnesota, Minneapolis, MN*
11:40 - 12:00 PM	***Panel Discussion***
Session II: Molecular Mechanisms of Senescence *Moderators: Mansoor M Ahmed, NCI, and Jorg Goronzy, Stanford*	
12:00 - 12:15	Intercellular communication in senescence and aging; Ana O'Loghlen, *Queen Mary University, London, UK*
12:15 - 12:30	DNA damage response regulating senescence and immune response; Alexandros Georgakilas, *National Technical University of Athens, Greece*
12:30 – 12:45	Immunosenescence; Jorg Goronzy, *Stanford University, CA*
12:45 – 1:05	***Panel Discussion***
1:05 - 1:45	***Lunch***

Session III: Metabolic and Epigenetic Mechanisms *Moderators: Pataje Prasanna, NCI and Stephen Kron, University of Chicago*	
1:45 - 2:00	Long-term senescence in endothelial cells through mitochondrial respiratory complex dysfunction; Francois Paris, *University of Nantes, Nantes, France*
2:00 - 2:15	Sirt family of proteins in the modulation of ROS, carcinogenesis and aging; David Gius, *Northwestern University, Chicago, IL*
2:15 - 2:30	Escape from chemotherapy and radiation-induced senescence: Impact of senolytics and tumor dormancy; David Gewirtz, *Virginia Commonwealth University, Richmond, VA*
2:30 - 2:45	Chromatin modifications linking DNA damage to senescence; Stephen Kron, *University of Chicago, Chicago, IL*
2:45 – 3:05	***Panel Discussion and Wrap Up Day 1***

Day 2, August 11, 2020

9:15 -9:30	**Arrival**
	Session IV: Radiation, Senescence, and Tissue Remodeling *Moderators: Michael Espey and Deborah Citrin, NCI*
9:30 - 9:45	Mechanistic insights into the plasticity of cancer cells; Clemens A Schmitt, *Charité – Universitätsmedizin and Max-Delbrück-Center for Molecular Medicine, Berlin, Germany*
9:45 - 10:00	Cellular plasticity, minimal residual disease, and tumor recurrence in cancer; Mohamed Abazeed, *Northwestern University, Chicago, IL.*
10:00 - 10:15	Radiation-induced premature senescence; Daohong Zhou, *University of FL, Gainesville, FL*
10:15 - 10:30	Radiation, senescence, and tissue fibrosis; Deb Citrin, NCI
10:30 - 10:50	***Panel Discussion***
Session V: "One-Two Punch" Cancer Therapy *Moderators: Sundar Venkatachalam, NCI and Daohong Zhou, University of FL*	
10:50 - 11:05	Clinical translation of senotherapeutics; James Kirkland, *Mayo Clinic, Rochester, MN*
11:05 - 11:25	The SASP associated with therapy-induced senescence recruits antitumor TILS into the tumor microenvironment; Ann Richmond, *Vanderbilt University, Nashville, TN*
11:25 - 11:40	Cancer therapy, senescence, and antitumor immunity; Paul Romesser and Scott Lowe, *Memorial Sloan Kettering Institute, New York, NY.*
11:40 – 11:55	Strategies to target senescence; Jesus Gil, *MRC Imperial College, London, UK.*
11:55 – 12:15 PM	***Panel Discussion***
12:15 - 12:45	***Lunch***
	Session VI: Development of Senotherapeutics *Moderators: Gabriela Riscuta, NCI and Dan Xi, NCI*
12:45 – 1:00	Discovery and development of senotherapeutic agents for clinical translation; Guangrong Zheng, *University of FL, Gainesville, FL*

1:00 – 1:15	Chemoprevention and senescence, Marc Mendonca, *Indiana University, Indianapolis, IN*
1:15 – 1:30	Prevention of glioblastoma recurrence after radiotherapy by the elimination of senescent astrocytes; Sundeep Burma, *University of Texas Health, San Antonio, TX*
1:30 – 1:45	Regulatory considerations: Mitchell Anscher, *Food and Drug Administration, Silver Spring, MD.*
1:45-2:00	***Panel Discussion***
2:00 – 2:30	***General Discussion, Next Steps, Adjourn*** Moderators: Deb Citrin, *CCR, NCI* and Daohong Zhou, *University of FL, Gainesville, FL*

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Abstracts

Cellular Plasticity, Minimal Residual Disease, and Tumor Recurrence in Cancer

Mohamed Abazeed
Northwestern University,
Chicago, IL.

Small cell lung carcinoma (SCLC) represents one of the most intractable human cancers to therapeutic cures. It is an aggressive, tobacco-associated tumor with neuroendocrine features characterized by rapid growth, metastatic progression, and initial response followed by almost invariable resistance to therapy. Studies to date have not resolved the extent that diverse transcriptional programs drive SCLC and contribute to its lethality. We have identified distinct and commutative transcriptional states that confer complimentary functional attributes in individual SCLC tumors. We combine an integrative approach including high-resolution measurement of cell state dynamics at the single cell level and correlative studies using human-derived xenografts and clinical outcomes. We show that individual SCLC tumors display distinctive equilibria in the proportion of cells in well-delimited cellular states. We also show that phenotypic switching and transcriptional reprogramming represent critical mechanisms for SCLC persistence during chemotherapy, ultimately leading to treatment resistance and aggressive recurrence. New therapeutic strategies using drugs that modulate the epigenome alter population proportions and, accordingly, alter the responses of SCLC to chemotherapy in human *ex vivo* cultures and patient-derived xenografts. Overall, our results contribute to the understanding of a poorly characterized aspect of cancer heterogeneity, reveal single-cell behaviors promote phenotypic equilibrium in cancer populations, and propose new therapeutic strategies in this highly lethal disease.

Regulatory Considerations

Mitchell Anscher
Food and Drug Administration,
Silver Spring, MD, USA

The US Food and Drug Administration is charged with protecting the public health by ensuring the safety and efficacy of drugs, biologics and medical devices, and by ensuring the safety of products that emit radiation. Studies involving radiation therapy present unique regulatory challenges, especially when combined with drugs/biologics. This challenge arises due to the different toxicity profiles and timelines for the development of adverse events between radiation and systemic therapies. In general, the most concerning toxicities from radiation are late effects, usually defined as those persisting and/or occurring more than 90 days after radiation exposure. This phenomenon also presents challenges in trial design, especially for dose escalation trials where it is often impractical to consider late toxicities. In this session, we will present an overview of the drug development process, with an emphasis on the parts of the process that may be most relevant to the translation of senotherapeutics into the clinic. We will also address trial design strategies that may be especially pertinent to studies involving radiation therapy.

Radiation, Senescence, and Diseases

Stephen Brown
Henry Ford Health Systems
Detroit, MI

Senolytic drugs, agents that selectively induce death of senescent cells, are being developed to counter the effects of aging and the pathology of multiple chronic diseases. Radiation is one of the stress factors that induce cellular senescence, and indeed radiation exposure is a widely used laboratory tool to induce cellular senescence in a variety of diseases. We present exciting data that senolytics mitigate late radiation injury without protecting cancer from the damaging effects of radiation. The field of study would benefit from cell culture studies that realistically mimic the chronic damage observed in animal models of human disease. Many questions remain unanswered including the identification and characterization of appropriate endpoints and assays of cellular senescence. This presentation is designed to stimulate discussion and future investigation toward this goal, to reduce our gaps in knowledge and address the limitations of current laboratory approaches.

Elimination of Senescent Astrocytes in the Brain Tumor Microenvironment Attenuates Glioblastoma Recurrence After Radiotherapy

Eliot Fletcher-Sananikone, Yi Du, Nozomi Tomimatsu, Andrea Gilbert, Bipasha Mukherjee, and Sandeep Burma
Department of Neurosurgery, Department of Biochemistry and Structural Biology,
Mays MD Anderson Cancer Center,
UT Health, San Antonio, TX, USA

Glioblastomas (GBM) are lethal brain tumors for which ionizing radiation (IR) remains the mainstay of therapy. However, these tumors inevitably recur, and the recurrent tumors are highly therapy resistant. During GBM therapy, both the tumor and the surrounding brain tissue are irradiated with 60 Gy of IR. IR induces senescence in multiple cell types, and senescent stromal cells are known to promote the growth of neighboring tumor cells by secreting cytokines which create a senescence-associated secretory phenotype (SASP). We hypothesize that IR-induced senescence of normal brain cells in the tumor microenvironment is a powerful driver of GBM recurrence. We intra-cranially irradiated C57BL/6J mice and found that irradiated brains exhibited widespread senescence by 30 days post-IR, with the astrocytic population being highly susceptible. Genomic analyses of irradiated brains revealed an altered transcriptomic profile which included upregulation of *CDKN1A* (p21), a key enforcer of senescence, and increased expression of bona fide SASP proteins including HGF, the ligand for the RTK Met. We orthotopically implanted mock-irradiated or irradiated mice, at 30 days post-IR, with a limiting number of syngeneic glioma cells. Pre-irradiation of mouse brains resulted in a striking increase in tumor growth rates, with the resulting tumors showing a more aggressive phenotype and activation of Met. Importantly, irradiated p21-/- mouse brains did not exhibit SASP and failed to promote tumor growth, substantiating the link between IR-induced, p21-driven senescence and GBM development. Irradiated primary astrocytes underwent senescence in vitro and could promote the migration of glioma cells, and this could be attenuated with HGF-neutralizing antibodies or by the Met inhibitor Crizotinib. These findings indicate that SASP factors (like HGF) in the irradiated brain microenvironment could drive GBM recurrence after radiotherapy via the activation of RTKs (like MET) in the tumor cells. Significantly, we found that senolytic drugs can selectively kill senescent astrocytes both in vitro and in vivo resulting in decreased HGF levels and attenuated growth of glioma cells. Finally, we immunostained biopsies from brain tumor patients who had undergone radiotherapy for senescence markers. We found evidence of rampant senescence in nonneoplastic brain cells adjacent to human brain tumors corroborating our findings of radiation-induced senescence in the mouse brain. These findings indicate that adjuvant therapy with senolytic drugs following radiation might attenuate GBM recurrence. We are currently testing the validity of this therapeutic approach in pre-clinical mouse GBM models.

Senescent Cells as Both Drivers and Suppressors of Radiation-Induced Cancers

Judith Campisi
Buck Institute for Research on Aging and Lawrence Berkeley National Laboratory,
Novato, CA

Among the serious effects of many types of radiation, whether environmental or therapeutic, is DNA damage. Arguably, the most serious type of damage is DNA double strand breaks, which are also caused by many anti-cancer chemotherapies. And among the serious physiological effects of radiation exposure is a significantly increased risk for the development of cancer. This increased cancer risk is the result of two processes -- the cell autonomous acquisition of potentially oncogenic mutations owing to unrepaired or mis-repaired DNA damage (initiation), and the largely cell non-autonomous *response* to DNA damage known as cellular senescence (promotion). Senescent cells are thought to promote cancer progression through their senescence-associated secretory phenotype (SASP), which recent large-scale genomic and proteomic evidence indicates is surprisingly heterogeneous and dynamic. Further, the SASP can both fuel and retard cancer development, the latter mostly through activation of innate immune responses. Although therapeutic strategies are now being developed to selectively eliminate senescent cells, a major challenge will be to distinguish those senescent cells that promote or retard tumorigenesis, and then selectively target the cancer promoting senescent cells.

Radiation, Senescence, and Tissue Fibrosis

Deborah Citrin
Center for Cancer Research,
National Cancer Institute,
Bethesda, MD, USA.

Cellular senescence has been implicated in fibrotic processes in multiple organs. Senescence of stem cells and mesenchymal cells has been associated with altered tissue dynamics, disrupted regenerative capacity, pro-fibrotic inflammation, matrix deposition, and impaired tissue homeostasis. Radiation injury is characterized by progressive cellular senescence, a finding evident in a range of tissue types. Radiation injury models provide a unique opportunity to study the impact of cellular senescence on the processes associated with fibrotic diseases given the chronic, progressive, and irreversible natural history of these models.

DNA Damage Response Regulating Senescence and Immune Response

Alexandros G. Georgakilas
DNA Damage Laboratory, Applied Physics Department,
National Technical University of Athens (NTUA), Greece

There is accumulating evidence for a strong communication between DNA damage response (DDR) and triggering of immune response (ImmR) pathways. Upon irradiation with ionizing radiation (IR) from X-rays to particle radiation, induction of closely spaced DNA lesions forming clusters of damage (complex damage) is anticipated. These combinations of different types of damage from double strand breaks (DSBs) to a variety of non-DSB lesions impose a genuine stress to the cell and are considered repair resistant leading to several mainly detrimental effects. After biological damage, damage associated molecular patterns (DAMPs) are released instigating innate immune response. It is currently still unknown the range of this multifaceted biological effects but mutations, senescence and apoptosis are the most expected ones. In addition, the exact repair pathways followed are still debated. My presentation will focus on the idea of complex DNA damage as the main triggering event of biological effects and especially the current status of knowledge on how DDR induction may regulate the decision between senescence or apoptosis. In addition, studies from our lab will be presented on the interaction between DDR and ImmR.

Escape from Chemotherapy and Radiation-Induced Senescence: Impact of Senolytics and Tumor Dormancy

David Gewirtz
Virginia Commonwealth University,
Richmond, VA

Our laboratory (as well as others in the field) have demonstrated that senescence induced by chemotherapy and radiation in tumor cells is not irreversible, but indicative of a prolonged and durable growth arrest from which (some) tumor cells can re-emerge and demonstrate self-renewal capacity. Interestingly, in cell culture studies from multiple laboratories and utilizing different experimental models, this escape tends to occur over a similar time frame, generally within a period of 9-10 days after the induction of senescence arrest. A fundamental question is what changes in the cells or regulatory factors determine the capacity of the cells to undergo this recovery?

The entry into senescence and recovery from senescence have more than passing similarities with tumor dormancy and disease recurrence. Both senescent tumor cells and dormant tumor cells are growth arrested but viable and maintain the capacity to recover under the appropriate environmental conditions. A current challenge is to design an experimental model to examine whether, in fact, senescence might reflect one form of tumor dormancy, as the basis for tumor dormancy and disease recurrence in patients represents one of the major challenges facing the cancer research community.

Given the emerging consensus that therapy induced senescence is an undesirable outcome, there has been growing interest in the potential inclusion of senolytic agents in cancer therapeutics with the goal of eliminating senescent tumor cells. This approach could prevent proliferative recovery, delay the development of resistance and have a direct impact on disease recurrence. However, as with virtually all cancer therapies, this approach has drawbacks and limitations; furthermore, it is unclear whether the senolytics are tumor/therapy specific.

Strategies to Target Senescence

Jesus Gil
MRC Imperial College
London, UK

Cellular senescence is a complex stress response playing a causal role in many age-related pathologies. Promising strategies aimed at clearing senescent cells are potentially able to slow down the ageing process. To identify novel senolytic compounds, we have screened libraries comprising ~2,000 small molecules using systems of oncogene-induced and therapy-induced senescence. We have assessed the senolytic effect of these compounds in different cell types and in response to different senescent inducers. Interestingly, we observed that while some compounds have just selectivity to kill cells undergoing oncogene-induced senescence, others behaved as broad-spectrum senolytics. Here, we will show our progress on validation of one of these small molecules that displays conserved senolytic activity across different senescence models. So far, our results suggest the on-target activity of this compound and members of its family. Additional experiments are being conducted to gain mechanistic insights into the underlying signaling pathways involved. Moreover, preliminary results show the ability of this compound to selectively kill senescent cells in vivo in the context of natural ageing, therapy-induced senescence, and oncogene-induced senescence. Overall, our results suggest drug screens are a useful tool to identify new vulnerabilities of senescent cells and highlight the broad potential of senolysis as a therapeutic strategy.

Sirt Family of Proteins in the Modulation of ROS, Carcinogenesis, and Aging

David Guis
North Western University,
Chicago, IL,USA

Our work addresses a fundamental issue in oncology, namely, that age represents a strong cancer risk factor. We focus on the biology of the sirtuin (SIRT) gene family and have developed murine models connecting the organismal physiology of aging and metabolic bioenergetics to carcinogenesis and tumor cell resistance. Dysregulation of antioxidant and energy regulating enzymes leads to perturbations in metabolic homeostasis and the accumulation of oxidized metabolites and reactive oxygen species that adversely affect cellular metabolism. My laboratory has focused on understanding cell and mitochondrial networks that help maintain metabolic homeostasis and that, when disrupted, trigger early events in tumorigenesis and tumor cell resistance. We have made several foundational discoveries in this area, most notably, that *Sirt3* functions as a tumor suppressor (*Cancer Cell*) by controlling a key switch in manganese superoxide dismutase (MnSOD) activity (*Mol. Cell*). Recently, we identified a novel mitochondrial signaling axis, which when dysregulated, leads to aberrant cellular metabolism (*Nature Comm*.), lineage plasticity (*PNAS*), and tumor permissive/therapy resistant phenotypes. Our insights into mitochondrial biology, through lysine acetylation mediated by SIRT3, accords us the unprecedented opportunity to define the complex relationship of aging, oncogenesis, and drug resistance phenotypes. Specifically, we will use murine models altered for Sirt3-mediated deacetylation of MnSOD and Acetyl-CoA synthetase-2 to help fill major knowledge gaps. We will also conduct a clinical trial of the FDA-approved MnSOD chemical mimetic GC4419 that we have shown to reverse the tumor permissive phenotype of *Sirt3* and *MnSOD* cell culture and mouse models. We are confident that the knowledge garnered from our endeavors will allow medical practitioners to counsel patients, identify likely responders to therapy, predict the durability of drug response, and explain acquired drug resistance.

Immunosenescence

Jorg Goronzy
Division of Immunology and Rheumatology,
Department of Medicine,
Stanford University, Stanford, CA.

With increasing age, old adults develop a state of immune dysfunction. Functional hallmarks are constitutive activation of innate immunity causing inflamm-aging and defective adaptive immunity resulting in poor antiviral responses and poor generation of memory after vaccination. The mechanisms underlying immune decline are broadly termed immunosenescence. The term is reminiscent of cellular senescence; however, it is misleading to interpret immune aging only as the accumulation of senescent cells. The major findings in immune aging are in immune cell replenishment and in cell differentiation, while the role of cellular senescence is less well defined. A common driver of immune aging is the extensive need for cell division in the immune system, which comes at two dimensions; homeostatic proliferation to maintain the system and clonal expansion in response to antigen.
The immune system is in constant demand for cellular replenishment to compensate for peripheral losses and cell death. For neutrophils, which have a short half-life, the body needs to produce $\approx 10^{10}$ cells/kg per day; for lymphocytes, which are more long-lived but are also more numerous because of their wider tissue distribution, the daily need is in the order of several billion cells. With minimal thymic activity after puberty, the vast majority of T cell generation comes from homeostatic proliferation of existing T cell populations that leads to telomere erosion. Naïve T cells divide about once every several years without any evidence for compromised proliferative potential or cellular senescence, however, they acquire signatures of T cell differentiation. Memory T cells divide more frequently, but again mostly maintain their proliferative potential.

Upon stimulation with antigen, naïve T cell respond with rapid clonal expansion undergoing 10 to 15 divisions within one to two weeks and differentiate into effector cells followed by clonal downsizing. At the peak response, proliferating naïve T cells from older adults show increased activation of DNA damage responses that at least in part determines the extent of T cell loss in the contraction phase. One mechanism is the increased expression of SIRT1 that is recruit to histone promoters, inhibiting histone expression during the early S phase. Delay in fork progression causes replication stress, activation of p53 target genes and induction of p21, but not p16. Older adults are poised to produce more short-lived and inflammatory effector T cells and fewer long-lived memory T cells. The population of cells that is most closely related to cellular senescence is terminally differentiated CD45RA effector T cells that are generated through repeated restimulation by latent viruses such as CMV and EBV. They lose the ability to proliferate, express p16, but hyperproduce inflammatory mediators in response to antigen as well as cytokines. This proinflammatory state may indicate cellular senescence but may also represent a further development of their effector state through the activation of transcriptional programs of NK cells.

Taken together, the adaptive immune system of old adults is prone to effector differentiation, which eventually can lead to cellular senescence in chronically restimulated T cells. In contrast to exhausted T cells, these cells are functional and contribute to antiviral immunity.

Clinical Translation of Senolytics

James L. Kirkland
Mayo Clinic,
Rochester, MN

Aging processes such as cellular senescence might make a “root cause” contribution to chronic diseases. Senescent cells (SC) accumulate with aging and at sites of etiology of many chronic diseases. SC can release factors that are pro-apoptotic, inflammatory, pro-fibrotic, cause stem cell dysfunction, and spread senescence, the senescence-associated secretory phenotype (SASP). Transplanting small numbers of SC into young mice, so that only 1/10,000 cells in recipients are transplanted SC, is sufficient to cause frailty, accelerated age-related disease onset, and early mortality. A report in 2004 showing caloric restriction causes both healthspan extension and delays SC accumulation prompted us to begin efforts to discover senolytic drugs, agents that selectively eliminate SC. We used a hypothesis-driven, mechanism-based strategy to discover senolytics, reasoning that senescent cell anti-apoptotic pathways (SCAPs) exist that defend SC against their own SASP, allowing SC to survive, despite killing neighboring cells. Senolytics cause SC apoptosis by transiently disabling these SCAPs. Because SC take weeks to re-accumulate, senolytics can be administered intermittently – a “hit-and-run” approach.

In mice, intermittent senolytic administration alleviates many conditions, including age- or diet-related cardiovascular dysfunction, liver fat and fibrosis in steatosis, bleomycin-induced pulmonary fibrosis, radiation damage, cognitive dysfunction, and osteoporosis. Senolytics delay frailty, chronic diseases, and early death caused by transplanting SC. In old mice, senolytics improve physical function, delay age-related diseases, and extend remaining lifespan. In pre-clinical models, senolytics alleviate complications of organ transplantation, radiation, and cancer treatment. As anticipated for agents targeting the fundamental aging mechanisms that are “root cause” contributors to multiple disorders, potential uses of senolytics are protean, potentially alleviating over 40 conditions in preclinical studies.

We review potential strategies for translation of senolytics into the clinic. In early trials, senolytics reduced fat tissue SC in patients with diabetic kidney disease, attenuated adipose tissue inflammation and fibrosis, decreased circulating SASP factors, and alleviated physical dysfunction in patients with idiopathic pulmonary fibrosis. Other clinical trials that are currently underway or about to begin are for childhood cancer survivors (who have an accelerated “accelerated aging-like” frailty and multi-morbidity phenotype), bone marrow transplant survivors (with a similar phenotype), physical dysfunction in elderly subjects with multi-morbidity, Alzheimer’s disease, age-related osteoporosis, osteoarthritis, improving outcomes after transplanting organs from old donors, and COVID-19. Senolytics might hold promise for delaying, preventing, or treating age-related disorders, but much more study is needed before they are used outside the context of clinical trials.

Chromatin Modifications Linking DNA Damage to Senescence

Steve Kron
University of Chicago,
Chicago, IL

A single dose of radiation is sufficient to drive otherwise immortal cancer cells to terminal senescent arrest. We have dissected pathways linking cellular damage to senescence and examined features that distinguish proliferating and senescent cells toward understanding how radiation mediates its beneficial and toxic effects. Our work has explored chromatin modifications such as γH2AX that form at sites of double strand breaks (DSBs) to understand their roles in DSB repair, checkpoint signaling and senescence.

Recently, we found that blocking DNA-PKcs is able to uncouple completion of DSB repair from resolution of the epigenetic marks. Our data indicate that DNA-PKcs serves a key role in checkpoint recovery once DSB repair is complete by inactivating ATM and thereby allowing cells to enter mitosis. In cells lacking DNA-PKcs activity, γH2AX foci persist even at repaired breaks, reflecting deregulation of ATM. The persistent checkpoint signaling due to activated ATM prevents normal completion of cell division, resulting in mitotic slippage and senescence. Remarkably, blocking DSB rejoining does not prevent DNA-PKcs from inactivating ATM, allowing cell division despite persistent DSBs, resulting in mitotic catastrophe. We infer that in the face of complex damage as produced by radiation, DNA-PKcs may similarly drive checkpoint adaptation. While this may promote cell death, aneuploid cells that survive may have increased malignancy.

We find that like DNA-PKcs inhibitors, many other existing drugs and neutraceuticals combine with radiation to promote foci persistence, though most appear to do so by delaying DSB repair. While searching for common mechanisms among diverse drugs, we identified glycolysis and glutaminolysis as key mediators of DSB repair and checkpoint response, linked to their roles in regulating epigenetic marks. In particular, the hexosamine biosynthetic pathway provides an attractive, druggable target. Serine/threonine O-GlcNAcylation regulates the stability and/or activity of many proteins linked to DSB repair, but our data suggest that the H3K27 methyltransferase EZH2 subunit of PRC2 may be a key mediator. Toward translation, we have shown that manipulating protein O-GlcNAcylation is able to modulate DSB repair and radiation responses *in vitro* and *in vivo*, suggesting a new approach to targeting cancer and protecting normal tissue. In turn, by increasing O-GlcNAcylation, cancer metabolic reprogramming may promote radiation resistance, genomic instability and immortality.

Chemoprevention of Radiation-Induced Carcinogenesis by Vitamin E and EGCG are Due to Induction of Increased Apoptosis and Senescence

Joseph W. Boone[1], Wilson Freije[1], Christina C. Huang[1], Erin McCammack[1], Helen Chin-Sinex[1], Anthony J. Borgmann[1], Ryan Dhaemers[1], Marc S. Mendonca[1,2]
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Treatment induced secondary malignancies after successful cure of primary tumors by radiation and chemotherapy are a known area of concern in cancer treatment. There is a critical need to identify chemopreventive compounds that reduce radiation-induced secondary malignancy that are both nontoxic and well tolerated with long term use. We investigated whether Vitamins C & E, EGCG, and Resveratrol altered ionizing radiation-induced cell killing and carcinogenesis in the hybrid human cell CGL1 assay. The molecularly characterized CGL1 assay allows simultaneous alterations of quantitative neoplastic transformation and cell survival, as well as the ability to determine potential underlying molecular processes of chemoprevention. Short term incubation of CGL1 cells with vitamins C & E, EGCG, and resveratrol prior to irradiation treatment did not show significant alterations to carcinogenic radiation induced neoplastic transformation. However, we found long-term treatment with 15 µM EGCG or 50 µM Vitamin E beginning 72 hours after 7 Gy irradiation significantly reduces radiation-induced neoplastic transformation frequency. We determined that Vitamin E suppressed radiation-induced carcinogenesis by the induction of a p53 and pro-apoptotic Bax dependent apoptosis in the progeny of the irradiated CGL1 cells. In addition, we demonstrated that EGCG does not reduce radiation-induced carcinogenesis by increased apoptosis but rather by the onset of p16 dependent senescence in the irradiated CGL1 progeny. Vitamin E and EGCG are excellent candidates of nontoxic chemopreventive agents that prevent radiation-induced carcinogenesis through two distinct molecular mechanisms. We propose that this information should also aid in the development of next generation chemopreventive compounds.

Senolytic and Senomorphic Therapy

Laura Niederhofer, M.D., Ph.D.,
University of Minnesota
Minneapolis, MN, USA

Senotherapeutics include drugs that selectively kill senescent cells (senolytics) and drugs that modify the senescence phenotype, primarily modifying their secretory phenotype. Senolytics, in particular, have proven efficacious in a remarkably diverse array of disease models. Senotherapeutics discovered to date, their applications, and method of discovery will be summarized. The remaining gaps in knowledge, such as frequency of administration, safety, applications and use of senolytics vs. senomorphics will be highlighted. From our own research, we've found that DNA damage is a potent driver of cellular senescence, but not in all cell types. Thus, radiation and genotoxic cancer therapy are clearly going to cause senescence and premature aging in cancer survivors. However, we also find that having an increased burden of senescent cells can dramatically exacerbate the response to a stressor, such as infection, leading to an altered immune response, cytokine storm and even death. Therefore, considering senotherapy prior to cancer therapy should be considered. Finally, we find that senescent immune cells are particularly potent in spreading senescence. Thus, monitoring levels of senescent immune cells during and after therapy may prove to be a valuable biomarker of patient outcomes.

Intercellular Communication in Senescence and Aging

Ana O'Loghlen
Epigenetics and Cellular Senescence Group,
Blizard Institute, Barts and The London School of Medicine and Dentistry,
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Aging is characterised by a functional decline of an organism where the correct performance of several tissues and cellular behaviour become affected. Several hallmarks have been identified in aging such as the activation of cellular senescence. Senescence is a cellular phenotype characterised by a stable cell cycle arrest and a particular secretome termed SASP (senescence-associated secretory phenotype). The best recognised components of the SASP are soluble factors that affects the function of neighbouring cells. However, other novel means of intercellular communication are recently emerging in senescence and aging such as the release of extracellular vesicles (EV). Extracellular vesicles are lipid-based vesicles released by most cells to the microenvironment containing biological material such as nucleic acids, proteins and lipids. Here, we will describe how extracellular vesicles can influence the behaviour of surrounding cells which varies depending on the context.

Long-Term Senescence in Endothelial Cells through Mitochondrial Respiratory Complex Dysfunction

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Endothelial cells are contributing to early and late response to normal tissue radiotoxicity. We previously demonstrated that irradiation of non-proliferating endothelial cells induces acute ceramide-dependent apoptosis, which is inhibited by Sphingosine 1-Phosphate (S1P) pretreatment. Because endothelial cells may survive after radiation, we aimed to investigate their chronic radiation response. Long term senescence was validated in irradiated quiescent microvascular HMVEC-L in dose- and time-dependent manner. Since no modulation was observed after S1P pretreatment, the aging process was not connected to apoptosis. Molecular actors in senescence were deciphered showing persistent activation of the p53 pathway and mitochondrial dysfunctions characterized by O2●- generation, inhibition of respiratory complex II activity, overexpression of prosurvival Bcl-xL, member of the Bcl-2 family. Inhibition of Bcl-xL with Navitoclax demonstrated a senolytic activity when pifithrin–α, a p53 inhibitor, or MnTBAP, a SOD mimetic, showed senomorphic properties on radiation-induced endothelial aging. MnTBAP, but not pifithrin–α, was able to block O2●- generation and to rescue a respiratory complex II activity. Furthermore, MnTBAP was not inhibiting p53 over-expression, suggesting radiation-induced senescence in quiescent endothelial cells, where mediated by at least 2 independent molecular pathways. Further characterization of the actors involved in the respiratory complex II dysfunction, will open new pharmacological strategies to modulate late radiation toxicity.

The SASP Associated with Therapy-Induced Senescence Recruits Anti-Tumor TILS into the Tumor Microenvironment

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Tumor cell senescence is a common outcome of anticancer therapy. Moreover, therapy-induced senescence (TIS) affects tumor-infiltrating leukocytes (TILs) and the efficacy of immunotherapy in melanoma. Using inhibitors of AURKA or CDK4/6 alone or combined with MDM2 antagonists that stabilize p53 we have produced TIS. AURKA inhibitor response is associated with induction of the immune transcriptome ($P = 3.5 \times 10^{-29}$) while resistance inversely correlated with TIL numbers (Spearman $r = -0.87$, $P < .001$). AURKAi and CDK4/6i promoted the recruitment of TILs by inducing CCL5 secretion in melanoma cells ($P \leq .005$) in an NF-κB-dependent manner. Therapeutic response to AURKAi is impaired in immunodeficient compared with immunocompetent mice (0% vs 67% tumors regressed, $P = .01$) and in mice bearing CCL5-deficient *vs.* control tumors ($P = .61$ vs $P = .02$); however, AURKAi response is greatly enhanced in mice also receiving T-cell-activating immunotherapy ($P < .001$). In human tumors, expression of chemokines that induce T cell migration is also induced by AURKAi ($P \leq .02$) and CDK4/6i ($P = .01$) and is associated with increased immune marker expression ($P = 1.40 \times 10^{-93}$).The senescence associated secretory protein component of senescent melanoma cells may include chemokines such as CCL4, CCL5, CXCL9, CXCL10, and CXCL11, which promote recruitment of TILs and dendritic cells. Combining TIS with immunotherapy that enhances tumor cell killing by TILs is a promising novel approach to improve melanoma outcomes. On the other hand, depending upon the therapy used, the TIS-associated SASP of senescent tumor cells may recruit myeloid-derived suppressor cells, M2-like macrophages, and T-regulatory cells, which requires approaches like co-treatment with inhibitors of CXCR2, CXCR4, CCL2, and/or CCL3. Thus, the cytokine/chemokine secretion profile associated with the SASP of TIS will determine what type of biological therapy to combine with the senescence inducing therapy. Interestingly, nevi bearing BRAF or NRAS mutations exhibit oncogene induced senescence (OIS), but seldom exhibit TIL recruitment. Thus, the SASP of OIS may differ from that TIS and this will be an important comparison to study.

Cancer Therapy, Senescence, and Antitumor Immunity

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Cellular senescence limits proliferation of damaged and premalignant cells and can be triggered in response to diverse forms of cellular stress. Senescent cells undergo a stable cell cycle arrest that involves interplay between RB and p53 tumor suppressors leading to a transcriptional program of gene repression that silences proliferation associated genes[3-5]. In addition, senescent cells upregulate mRNAs encoding secreted factors (including inflammatory cytokines, chemokines, and matrix metalloproteinases), a program collectively referred to as the senescence-associated secretory phenotype or SASP, that interacts with the tumor microenvironment[1, 6]. SASP proteins have been shown to have pleiotropic immune modulatory effects such as recruiting and activating natural killer (NK) cells[7, 8], altering macrophage polarization to kill and/or engulf senescent cells[9], and activating T cells[10]. Many common anti-cancer therapies induce senescence (*i.e.* ionizing radiation and genotoxic drugs), yet the clinical implications of therapy induced senescence is poorly defined. Pre-clinical work from our group has demonstrated that chemotherapy sensitivity is partially dependent on senescence induction[11], and more recently, we have demonstrated that targeted therapy that combines CDK4/6 and MEK inhibition can induce cellular senescence and activate an immune modulatory SASP. This in turn contributes to tumor regression and prolonged survival through activation of innate immunity in KRAS mutant lung cancer [12] and adaptive immunity in KRAS mutant pancreas cancer[13]. While ionizing radiation is known to induce cellular senescence[14-16], the contribution of ionizing radiation induced senescence and the resultant SASP to the anti-tumor response remains largely uncharacterized.

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Mechanistic Insights into the Plasticity of Senescent Cancer Cells

Clemens A. Schmitt (and colleagues)[1-3]
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[3] Max-Delbrück-Center for Molecular Medicine,
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Cellular senescence is a terminal cell-cycle arrest program evoked by various stresses, among them activated oncogenes and DNA-damaging anti-cancer agents in the context of (pre-) neoplastic lesions and full-blown malignancies. Although the proliferative cessation and the senescence-associated secretory phenotype (SASP) are acknowledged as hallmarks of the senescent condition, other features – in particular remodeled cellular phenotypes – are of pivotal functional relevance. In the past, we presented evidence for metabolic and stem-like remodeling in senescent cells; more recently, we obtained evidence for an immunogenic switch that renders senescent cells preferentially susceptible to an adaptive T-cell attack. Interestingly, therapy-induced senescent B-cell lymphomas exhibit cellular plasticity, i.e. lineage promiscuity towards myeloid trans differentiation. Given the dynamic nature of the senescent state and the occasional cell-cycle re-entry of previously senescent cells, plasticity-associated functional capabilities may become particularly relevant during the selective pressure of senescence evasion and tumor re-progression.

Protecting the Bone Marrow from Ionizing Radiation

Norman E. Sharpless
The National Cancer Institute, MD, USA.

Serial cyclic exposure to DNA damaging agents followed by bone marrow regeneration causes an iatrogenic form of accelerated hematopoietic aging ("bone marrow exhaustion"), which limits the success of cancer therapy and causes significant long-term morbidity. Pharmacological inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) induces a transient and reversible G1 cell cycle arrest in Hematopoietic Stem and Progenitor Cells (HSPCs). I will discuss clinical efforts to use this transient cell cycle arrest to decrease the toxicity of DNA damaging agents. Human data suggests this approach works well to ameliorate the acute multi-lineage myelosuppression from cytotoxic chemotherapy. Murine data suggests this approach can also protect the long-term function of hematopoietic stem cells (HSCs), such as their long-term multilineage reconstitution potential and the ability to efficiently generate lymphoid progenies. Although these studies are more advanced for pharmacological agents that induce DNA damage, I will focus on the prospects of this approach for reducing acute and long-term IR toxicity.

Animal Models to Study the Role of Senescent Cells in Diseases and Cancer

Naomi Hamada, Shawn Trewartha, Bennet Childs, Ines Sturmlechner, Darren Baker, and Jan van Deursen,
Rochester, MN

In mice, selective elimination of SNCs (senolysis), extends median lifespan and prevents or attenuates various features of aging and diseases without exerting overt adverse side effects. These findings have inspired the development of senolytic drugs to safely eliminate the SNCs that drive tissue degeneration and disease in humans. However, newly recognized beneficial signalling functions of SNCs in tissue repair and regeneration suggest that indiscriminately targeting senescent cells or modulating their secretome for anti-aging therapy may have negative consequences. To study beneficial and detrimental SNCs in vivo, we created a new mouse model that allows for the visualization, tracking and in-depth characterization of SNCs in tissues and organs. This model has been extensively validated and used for detailed characterization of SNCs that accumulate in kidney with aging, including assessment of the cell types of origin, molecular and functional evolution, and ability to invoke immunosurveillance. Application of the mouse model to characterize the identity and the properties SNCs that accumulate in the context of cancer will also be discussed.

Discovery and Development of Senotherapeutic Agents for Clinical Translation

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Pharmacological elimination of chronically accumulated senescent cells by senolytics has emerged as a promising therapeutic approach. Many senolytics have been identified and some of these have successfully entered clinical trials. However, novel senolytics are still needed in order to treat a diverse range of age-related diseases. We have been investigating several approaches to identify senolytics that can more safely and effectively target senescent cells. In one study, we apply activity-based proteomics approach for the identification of novel senolytic targets through piperlongumine-based probes. In another study, we apply the Proteolysis Targeting Chimera (PROTAC) technology to design small-molecules that target Bcl-xL for degradation. This proof-of-concept study demonstrates the potential application of PROTAC approach to more specifically target senescent cells.

Radiation-Induced Premature Senescence

Daohong Zhou
University of Florida,
Gainesville, FL

Cellular senescence is an important tumor-suppressive mechanism because it permanently arrests the proliferation of damaged and genetically deranged cells and promotes their removal by the immune system. However, if senescent cell (SnC) production exceeds the immune clearance capacity or the immune system cannot efficiently remove SnCs, SnCs can accumulate in tissues; this occurs after exposure to ionizing radiation (IR) and during aging. Accumulation of SnCs can contribute to many IR-induced normal tissue injuries and age-related diseases including cancer by disrupting tissue structures and functions and accelerating tissue stem and progenitor cell exhaustion directly and indirectly by secreting inflammatory cytokines and many other factors, termed the senescence-associated secretory phenotype (SASP). In addition, SnCs create a tumor promoting microenvironment that can facilitate tumor resistance, recurrence and metastasis also in part via SASP after chemotherapy and radiation. Therefore, SnC production and clearance have to be tightly regulated in order to prevent SnC accumulation to improve tumor response to therapy, reduce radiation-induced late effects, and extend the healthspan. New strategies and potential therapeutics such as senolytics that can effectively clear senescent cells and suppressing SASP and their applications will be also discussed in this talk.

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BIOSKETCHES

Mohamed Abazeed
Northwestern University,
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Dr. Abazeed is a radiation oncologist and physician scientist who uses trans-omic approaches in order to improve the personalization of cancer treatments. His clinical research efforts are focused on improving therapies for lung cancers, including the initiation of investigator-initiated theranostic studies. He has made several contributions to identifying tumor mutations that predict resistance to therapy. Using his training and background in computational biology, genetics, and imaging, he has also applied and developed tools to advance approaches for personalized cancer treatment, especially for patients treated with ionizing radiation. His cancer biology research efforts are focused on improving our understanding of tumor development and overcoming treatment resistance. Supporting his group's translational efforts is the development of large-scale clinomic datasets (~1000 cases) that integrate detailed clinical information, patient-derived xenografts, and genomic features. His team routinely employs tools from genomics, bioinformatics, computational modeling, and tumor biology in their work. Dr. Abazeed is currently an associate professor at Northwestern University's Feinberg School of Medicine, the Scientific Director of the Lung Cancer Program, and the inaugural Director of the Center for Precision Radiotherapy in the Department of Radiation Oncology. He received his MD/PhD degrees from the University of Michigan with a research focus in genetics. During his residency training at the Harvard Radiation Oncology Program, he was the *Leonard B. Holman Research Fellow* and conducted his training under the mentorship of Dr. Matthew Meyerson, a global leader in cancer genomics.

Mitchell S. Anscher, MD
Food and Drug Administration,
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Dr. Anscher is a Medical Officer at the U.S. Food and Drug Administration (FDA). Prior to joining the FDA, Dr. Anscher served as Professor and Genitourinary Section Chief in the Department of Radiation Oncology at the University of Texas M.D. Anderson Cancer Center, Florence and Hyman Meyers Professor and Chair of the Department of Radiation Oncology at Virginia Commonwealth University, and Professor and Clinical Director in the Department of Radiation Oncology at Duke University. He is board certified in both Internal Medicine and Radiation Oncology. His research interests included clinical trials in Genitourinary malignancies and molecular/translation research into normal tissue injury following cancer therapies. He has published over 300 research articles, reviews, book chapters, abstracts and 3 books. He has lectured widely both in the U.S. and abroad and has served as visiting professor at numerous institutions. He was named one of America's Top Doctors for 20 consecutive years. He is a fellow of the American College of Radiology, American Society for Radiation Oncology and American College of Radiation Oncology. He has served on numerous national and international grant review committees, and on Program Committees for Annual Meetings of the Radiation Research Society and American Society of Radiation Oncology.

Stephen L. Brown, PhD
Radiation Oncology, Henry Ford Health System,
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Dr. Brown is the Director of the Radiation Biology Laboratories in the Department of Radiation Oncology at Henry Ford Health System in Detroit, MI. He serves as the Leader of Translational Oncology Laboratory Research at Henry Ford Cancer Institute in Detroit, MI. In addition, he is a Professor of Radiation Oncology at Wayne State University in Detroit, MI. Dr. Brown's formal training is in Medical Physics from University of Toronto, Canada. His laboratory is active in the translation of new technology and biology that has the potential to improve therapeutic gain of radiation therapy. He has explored new anti-cancer approaches, strategies to mitigate normal tissue inadvertently damaged by radiotherapy, and new imaging technologies to guide treatment using quantitative measures of physiology (blood flow, permeability, interstitial fluid pressure, etc.). He has been at Henry Ford Hospital for 30 years.

Sandeep Burma, Ph.D.
University of Texas Health,
San Antonio, TX, USA.

Dr. Burma holds the Mays Family Foundation Distinguished Chair in Oncology, is Professor of Neurosurgery and of Biochemistry & Structural Biology, and the Vice Chair for Research in the Department of Neurosurgery at UT Health San Antonio. He is also a member of the Mays MD Anderson Cancer Center at UT Health. Before moving to San Antonio, he spent fourteen years at the UT Southwestern Medical Center where he developed a strong research program in DNA double-strand break repair and radiation resistance in glioblastoma. Dr. Burma obtained his doctoral degree from the National Institute of Immunology in India.

After postdoctoral research in the fields of transcription and DNA repair at Yale University, Pennsylvania State University, and the Los Alamos National Laboratory, he worked as a Career Scientist at the Lawrence Berkeley National Laboratory. He started his own research laboratory at UT Southwestern in 2005 and rose through the ranks there to become Professor of Radiation Oncology in 2019.

At UT Health San Antonio, Dr. Burma continues to focus his basic research on the responses of mammalian cells to ionizing radiation with an emphasis on DNA end resection and repair pathway choice. His translational research is focused on glioblastoma recurrence after radiotherapy with an emphasis on the role of senescence in driving recurrence. Dr. Burma is also involved in the educational missions of UT Health through teaching and his mentorship of students in the Graduate School of Biomedical Sciences, and students and residents in the Long School of Medicine.

Judith Campisi
Buck Institute,
Novato, CA, USA.

Judith Campisi received a PhD in biochemistry from the State University of New York Stony Brook, and postdoctoral training in cancer biology at the Dana-Farber Cancer Institute. In 1984, she joined the Boston University Medical School faculty as Assistant and Associate Professor, then joined the Lawrence Berkeley National Laboratory as Senior Scientist in 1991. In 2002, she started a second laboratory at the Buck Institute for Research on Aging, where she is Professor.

At both institutions, Campisi established a broad program to understand the relationship between aging and disease, with an emphasis on the role of cellular senescence in promoting inflammation, cancer and degenerative diseases. Her laboratory made several pioneering discoveries in these areas.

Campisi has received MERIT awards from the National Institute on Aging, and awards from the AlliedSignal Corporation, Gerontological Society of America and American Federation for Aging Research, the Longevity prize from the IPSEN Foundation, and the first international Olav Thon Foundation prize. She is an elected fellow of the American Association for the Advancement of Science, American Association for Cancer Research, and a member of the National Academy of Sciences. She serves on numerous national and international editorial and advisory boards.

Deborah Citrin
Center for Cancer Research,
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Dr. Deborah Citrin is a clinician and translational researcher in the Intramural Radiation Oncology Branch at the National Cancer Institute (NCI) in Bethesda, Maryland. She is a graduate of the Duke University School of Medicine and completed her residency training at the NCI. She is currently a Senior Investigator in the Radiation Oncology Branch and a Deputy Director of the Center for Cancer Research. Her research interests include understanding how certain tumors can become resistant to cell killing by radiation and understanding the mechanisms of normal tissue injury from radiation. Dr. Citrin's laboratory is focused on damage in tissue exposed to radiation through stem cell senescence. Her laboratory is focused on the impact of radiation-induced senescence on parenchymal depletion, immune cell phenotype, and tissue dynamics.

Clemens A. Schmitt, M.D.
Professor of Hematology and Oncology,
University Medical Center,
Berlin, Germany

Clemens A. Schmitt, M.D., is a hematologist/oncologist, especially a lymphoma specialist, who directs the medical department of hematology/oncology at Kepler University, Linz, Austria, is co-affiliated as a principal investigator with the Charité – University Medical Center and the Max-Delbrück-Center for Molecular Medicine in Berlin, Germany, and has a long-standing record as a clinician scientist with a strong translational research background in lymphoma, cellular senescence and stem cell biology. His work, published in journals like *Nature*, *Cell*, *Nature Medicine* and *Cancer Cell*, includes landmark *in vivo* findings on oncogene-induced senescence as an anti-tumor barrier, therapy-induced senescence as a major contributor to long-term outcome, senescence-associated metabolic vulnerabilities and their targeting as a first demonstration of an effective "senolytic" therapy, the highly dynamic (and, hence, not necessarily irreversible) nature of senescence, and epigenetic stemness reprogramming as a particular critical feature of tumor cell senescence. Moreover, he serves as the principal investigator in numerous clinical trials, including a senescence- and functional mouse modeling-inspired multi-center 1st-line lymphoma trial that explores four different treatment modalities by obtaining re-biopsies acutely under and in the later course of therapy to determine molecular signatures of response, and seeks to mechanistically dissect patient responses to individual treatment components in flanking patient-derived xenograft models. Clemens Schmitt also coordinates several collaborative research projects and is a member of numerous scientific steering committees and advisory boards.

Alexandros G. Georgakilas
DNA Damage Laboratory, Physics Department, School of Applied Sciences,
National Technical University of Athens,
Greece

Research interests: Radiation Biology, DNA Damage and Repair, Biomarker discovery for efficient radiation therapy, Bioinformatics

Dr. Alexandros Georgakilas is currently an Associate Professor in the Department of Physics, School of Applied Mathematics and Physical Sciences, National Technical University of Athens (NTUA), Greece. At Brookhaven National Laboratory, USA, Dr. Georgakilas completed post-doctoral research as a research associate in the Biology Department from 2001-2003 under the supervision of Dr. Betsy Sutherland and developed his own research laboratory as an **Associate Professor** with tenure at Biology Department of East Carolina University until 2012. Overall, Dr. Georgakilas has been an active non-stop researcher in the field of Radiation Biology for more than twenty (25) years.

He has also received awards such as the Young Investigator Travel Award from Radiation Research Society, Radiation Research Society SIT Award, ECU Thomas Harriot College Research Award, and the prestigious Terashima Award from Japan Radiation Research Society. His work at ECU as Principal Investigator (PI) has been funded by various sources like East Carolina University, NCI, NC Biotechnology Center and Union for International Cancer Control (UICC). His quality research work has been published in more than one hundred (100) peer-reviewed high profile journals like Genome Biology, Seminars in Cancer Biology, Radiation Research, Cancer Letters, Cancer Research, Pharmacology and Therapeutics, Free Radical Biology and Medicine, Journal of Cell Biology and Proceedings of National Academy of Sciences USA and more than 6700 citations. In addition, he has been able to produce already eight (54) publications from his laboratory at NTUA (Greece).

Last but not least and in recognition of his major contributions in the field he has been appointed the Editor-in-Chief in the Journal of Biochemical Technology 2012-2015, Associate Editor Position for Cancer Letters, Radiation Research and several other well-recognized journals. Dr. Georgakilas was invited as a Guest Editor for a Special Issue of Frontiers in Genetics, Seminars in Cancer Biology, Mutation Research, Cancer Letters and Current Molecular Medicine and has hold invited Editorial positions for different book projects (Science Publishers and InTech).

David Gewirtz
Virginia Commonwealth University,
Richmond, VA, USA.

Dr. Gewirtz received his PhD degree from Mt. Sinai School of Medicine of the City University of New York. He has been at Virginia Commonwealth University in the Department of Pharmacology and Toxicology and as a member of the Massey Cancer Center for his entire career. His work has been in the areas of cancer chemotherapy and radiotherapy, originally in breast cancer, but more recently extending to lung cancer, prostate cancer and head and neck cancer. His interests have long been in the nature of alternative tumor responses to therapy, most prominently autophagy and senescence. He has long argued that senescence is not an irreversible form of growth arrest, that senescence could represent one form of tumor dormancy and furthermore that recovery from senescence could contribute to disease recurrence. His most recent publication describes the impact of the senolytic agent, ABT-263 (navitoclax) on breast and lung tumor cells induced into senescence by cancer chemotherapy and radiation.

Jesus Gil
MRC Imperial College,
London, UK.

Jesús Gil was born in Zaragoza, Spain. He obtained his PhD studying how the dsRNA- dependent protein kinase induces apoptosis and activates NF-□B, in 2000 at the Universidad Autónoma in Madrid. From 2000 to 2003 he worked with David Beach at the Wolfson Institute for Biomedical Research, University College London, where he screened for genes bypassing senescence, identifying CBX7.

In January 2004, he joined Gordon Peters' group at the CRUK London Research Institute, investigating how CBX7 regulates the *INK4/ARF* locus. During 2005 he visited Scott Lowe's laboratory at Cold Spring Harbor, New York, developing models to study CBX7 function *in vivo*. Since Nov. 2005 he leads the Cell Proliferation Group at the MRC London Institute of Medical Sciences (MRC LMS) were his main interest is to understands how senescence is regulated. His laboratory has interest on epigenetic mechanisms controlling senescence (and more specifically regulating the *INK4/ARF* locus) and the senescence-associated secretory phenotype (SASP). To this end they use mammalian system of senescence and a variety of strategies to perform functional screens. The ultimate end is to understand the molecular mechanisms controlling senescence and exploit them for therapeutic benefit. In 2008, Jesús was named an EMBO Young Investigator. He got tenured in 2010 and in 2011 obtained the EACR Cancer researcher Award 'highly commended'. Since 2013 he is a Professor at Imperial College where it heads the Department of Molecular Sciences at the Institute of Clinical Sciences.

Jorg Goronzy
Division of Immunology and Rheumatology, Department of Medicine,
Stanford University,
Stanford, CA, USA.

Jörg J. Goronzy, MD, PhD is a Professor of Medicine at Stanford University School of Medicine. Before joining Stanford, he was the Mason I. Lowance, M.D. Professor of Medicine and Director of the Kathleen B. and Mason I. Lowance Center for Human Immunology at Emory University. From 1990 to 2003, he was on the faculty of the Mayo Medical and Graduate School. His expertise is in human immunology and in particular in the area of T cell repertoire maintenance and T cell function over lifetime. He is interested in the mechanisms that increase the susceptibility to develop autoimmune diseases such as rheumatoid arthritis and giant cell arteritis with age, while compromising the generation of protective immune responses. His recent studies are focused on identifying age-related defects in CD4 T cell activation and differentiation with the ultimate goal to define T cell-directed interventions that improve antiviral and vaccine responses in the elderly.

David Guis
North Western University,
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I am a first-in-family scholar, and I started my academic career with one year of junior college before transferring to the University of Illinois-Chicago (UIC), which at the time was a commuter university. I went on to obtain a B.S. in chemistry from UIC in 1983. From this point up through today, mentorship has been the foundation of my career successes. After two years at Loyola Medical School, the dean allowed me to take a leave of absence to attend the University of Chicago, where I received a D. Phil. degree in virology and worked with two of cancer biology's most respected mentors, Dr. Lou Laimins, who is now the Chairman of the Department of Microbiology and Immunology at Northwestern University, and Dr. Vikas Sukhatme, who is now the Dean of the Emory School of Medicine, and the Chief Academic Officer, Emory Healthcare Medicine. My dissertation research focused on how cis- and trans-acting DNA binding factors regulated HPV-18 gene expression and how immediate early signaling and/or transcription factors regulated HPV gene expression. After graduating from Loyola in 1992 with an M.D. degree, I did a radiation oncology residency/fellowship at the University of Michigan and Washington University, where I worked for Drs. Carlos Perez and Allan Lichter, two chairmen who helped guide my career development. During this time, my research focused on the mechanistic link between aberrant cell and mitochondrial oxidation metabolisms and the dysregulation of signaling factors involved in carcinogenesis, and the mechanisms that drive therapy resistance in tumor cells.
I started my independent laboratory in 2001 in the Radiation Oncology Branch of the NCI, and my career accomplishments were significantly enhanced at the direction of two of the NIH's best scientists and mentors, Drs. Jeff Trent and Doug Lowy. With their guidance, my laboratory extended its existing research interests in how tumors exploit aberrant changes in cell and mitochondrial oxidative molecules to evade the cytotoxicity of therapeutic agents, which include pathways that govern aging. Notably, by murine models and the examination of human tumor tissues, we showed that SIRT3 (Kim, 2010, *Cancer Cell*) and SIRT2 (Kim, 2011, *Cancer Cell*) function as tumor suppressors (TSs). We also showed, for the first time, that MnSOD detoxification activity is regulated by acetylation (Ac), and that MnSOD is a key downstream target in the tumor-permissive phenotype (Tao, 2011, *Mol. Cell*) observed in mice genetically deleted for the *Sirt3* gene. Recently, we showed that lysine 68 acetylation (K68-Ac) directs whether MnSOD functions in its established role as a tetrameric detoxification enzyme and tumor suppressor, versus its newly discovered role as a monomeric peroxidase that functions as a tumor promoter and to induce tumor resistance to therapeutic interventions (Zhou, 2019, *Nature Commun*.). Interestingly, we also showed that non-physiological levels of MnSOD-K68-Ac alter cell and mitochondrial metabolism, and increase levels of reactive oxygen species, leading to stem cell-like properties, suggesting the development of lineage plasticity through HIF2 activation (He, 2019, *PNAS*). This may be a mechanism linking altered cell metabolism and the observed tumorigenic and therapy-resistant phenotypes.
Since my first research article as a graduate student, I have published 135 research manuscripts and according to Scopus, have over 9,800 citations and an h-index of 53. When I was the Section Chief of Molecular Radiation Biology at the NCI, I served as the residency director (2005 – 2007), as a Member of the Cancer Therapy Evaluation Program committee (2001 – 2003), on the NCI IRB (2002-2006), as the Deputy Director of the NIH-Oxford-Cambridge (OxCam) graduate program, as Chair of the American Society of Radiation Oncology (ASTRO) Education and Research Committee (2008 – 2010), and was a member of the External Advisory Committee for the University of Virginia Cancer Center (2008 – 2011). During my current tenure at Northwestern University Feinberg School of Medicine, I have been on the chair recruitment committees for the Departments of Pharmacology, Biochemistry, and Cell Biology. I am the Director of the Women's Cancer Program (2016 – present), and the Co-PI of the recently

submitted (May 26th) Breast Cancer SPORE. In addition, I am the Chairman of the Internal Advisory Committee for the Pathology Core Facility, Robert H. Lurie Cancer Center, Feinberg School of Medicine Northwestern University; the Chairman of the Radiation Science and Medicine Working Group Steering Committee, American Association for Cancer Research (2017 – 2019); the Program Chair of the Cellular Stress Responses Section of the Molecular and Cellular Biology/Genetics Subcommittee, American Association of Cancer Research (AACR), Chicago, IL; and was a member of the Program Committee Member for the 2019 AACR Annual Meeting, Georgia World Congress Center, Atlanta, Georgia. At the 2019 AACR meeting, I presented in one of the featured symposia on "Sirtuins and Cancer." Finally, I was awarded the Radiation Oncology Teacher of the Year in 1998, while at Northwestern University I have been named a Member of the Alpha Omega Alpha (AOA) Honor Medical Society in 2014, and in 2018 I was named a
Fellow of the American Society of Therapeutic Radiation Oncology (FASTRO).
I am firmly committed to service, training, and mentorship of undergraduate and graduate students, residents, fellows, and post-doctoral fellows, and I take tremendous pride in my accomplishments in these areas as an academic faculty. In this regard, I have supervised well over 40 trainees/mentees who are routinely admitted into the most prestigious graduate and medical schools, and M.D./Ph.D. programs. In addition, 20 of my trainees are faculty members at medical schools including Washington University (3), Northwestern University (2), Emory University (2), University of Utah, University of Colorado, University of Washington, the National Cancer Institute, Columbia Medical School, Medical College of Wisconsin, University of Maryland, Roswell Park Cancer Center, University of Kentucky, Thomas Jefferson Medical School, Cedar Sanai Medical Center, Kyung Hee University, and the Natural Science Ewha Woman's University. Finally, twelve of my trainees are funded by the NCI to do cancer research.

James L Kirkland
Mayo Clinic,
Rochester, MN, USA.

James L. Kirkland, M.D., Ph.D., is Director of the Robert and Arlene Kogod Center on Aging at Mayo Clinic and Noaber Foundation Professor of Aging Research. Dr. Kirkland's research is on the contribution of fundamental aging processes, particularly cellular senescence, to age-related diseases and development of agents and strategies for targeting fundamental aging mechanisms to treat age-related chronic diseases and disabilities. Additional research areas include mechanisms of age-related adipose tissue and metabolic dysfunction, frailty, and loss of resilience to acute diseases in the elderly. Dr. Kirkland's laboratory published the first article about agents that clear senescent cells - senolytic drugs. Dr. Kirkland demonstrated that senolytic agents enhance healthspan and delay, prevent, or alleviate multiple age-related disorders and chronic diseases in mouse models. He published the first clinical trials of senolytic drugs and is currently conducting multiple clinical trials of senolytics. He has more than 200 publications and holds over 20 patents. Dr. Kirkland is PI of the Translational Geroscience Network (R33 AG061456), which brings together 8 academic institutions to translate healthspan interventions, including senolytics and other drugs that target fundamental aging processes, from bench to bedside. He is a scientific advisory board member for several companies and academic organizations. He is President-Elect of the American Federation for Aging Research, a past member of the National Advisory Council on Aging of the National Institutes of Health, and past chair of the Biological Sciences Section of the Gerontological Society of America. He is a board-certified specialist in internal medicine, geriatrics, and endocrinology and metabolism. Dr. Kirkland is the 2020 recipient of the Irving S. Wright Award of Distinction from the American Federation for Aging Research.

Steve Kron
University of Chicago,
Chicago, IL, USA.

Steve grew up near Philadelphia and attended the University of Pennsylvania for college and a masters degree, where his research was mostly in biophysics and bioengineering. He went on to Stanford for medical and doctoral degrees with the intention of learning molecular biology but ended up just doing more biophysics with Jim Spudich. As a post-doc at the Whitehead Institute at MIT, he finally got to manipulate genes, studying regulation of cell shape and cell division in yeast with Gerry Fink.
After setting up his lab at the University of Chicago, his group initially focused on how yeast cells respond to stress. Productive collaborations with Ralph Weichselbaum on radiation response helped the lab transition to modeling cancer both *in vitro* and in mice. Initially stimulated by "zombie" cells persisting after irradiation of cancer cells in culture and tumors, his lab has studied therapy-induced senescence for over a decade.
Steve is a professor of Molecular Genetics and Cell Biology and serves as chair of the Committee on Cancer Biology and director of the Cancer Biology PhD program. His lab has trained a couple hundred young scientists and has been generously funded by foundations, the NIH and other sources. Steve is an enthusiastic grant reviewer for NIH and other funders. He continues to develop new technologies, leading to patents and companies.

Marc S. Mendonca
Indiana University School of Medicine,
Indianapolis, IN, USA

Dr. Marc S. Mendonca is a Professor of Radiation Oncology & Medical and Molecular Genetics, and Director of Radiation and Cancer Biology at Indiana University School of Medicine. Dr. Mendonca has extensive expertise in both X-ray and proton radiation biology. Dr. Mendonca's research is focused on: 1) Understanding the mechanism of radiation-induced cancer and its prevention by natural antioxidants through alterations of apoptosis and senescence, and 2) Increasing the effectiveness of radiation in lung and pancreatic cancers by biochemical inhibition of NF-kappa B activity and Warburg metabolism, and physical approaches (protons, nanoparticles, and FLASH). Since 2011 Dr. Mendonca has served as the Editor-in-Chief of the journal *Radiation Research*. In April of 2020 Dr. Mendonca was appointed Associate Vice Chancellor for Research at IUPUI.

Laura Niederhofer, M.D., Ph.D.,
University of Minnesota,
Minneapolis, MN, USA

Laura Niedernhofer, M.D., Ph.D. is the Director of the Institute on the Biology of Aging and Metabolism at the University of Minnesota and Professor in the Department of Biochemistry, Molecular Biology and Biophysics. Her research program is focused on the development and translation of senotherapeutics. She trained at various points in her career at Duke, M.I.T, Georgetown, Vanderbilt and Erasmus Medical Center in Rotterdam, the Netherlands. She began her independent career in the cancer center at the University of Pittsburgh, then moved to the Scripps Research Institute, until transitioning to UMN in 2018. Dr. Niedernhofer's expertise is in DNA damage and repair. She is using murine models of genome instability to study the link between endogenous DNA damage, senescence and age-related diseases, and to test senotherapeutics.

Ana O'Loghlen
Epigenetics and Cellular Senescence Group,
Blizard Institute, Barts and The London School of Medicine and Dentistry,
Queen Mary University of London,
London, UK

Ana O'Loghlens' lab is based in London at the Blizard Institute which is part of Queen Mary University of London (UK). We are interested in understanding the molecular mechanisms regulating a cellular phenotype called "cellular senescence". Cells that become senescent stop growing and present a distinctive inflammatory response that has been termed senescence-associated secretory phenotype or SASP. The SASP induces a variety of cellular processes including immune cell recruitment, autocrine/paracrine senescence, differentiation and reprogramming. As senescent cells and the SASP are present during ageing and benign tumour lesions, we are interested in identifying new components of the SASP and investigating their role with the microenvironment in the context of ageing and cancer. Before starting her lab at Queen Mary, Ana trained as a post-doctoral fellow at the London Research Institute, Imperial College of London and the Spanish National Cancer Centre. She received her PhD from the Complutense University of Madrid.

Articles

1. Fafian-Labora et al (2020) Small Extracellular Vesicles Have GST Activity and Ameliorate Senescence-Related Tissue Damage. **Cell Metabolism** 32(1) 71-86

2. Borghesan, M. et al. (2019) Small Extracellular Vesicles Are Key Regulators of Non-cell Autonomous Intercellular Communication in Senescence via the Interferon Protein IFITM3. **Cell Reports** 27, 3956-3971.e6

3. Rapisarda, V. et al. (2017) Integrin Beta 3 Regulates Cellular Senescence by Activating the TGF-β Pathway. **Cell Reports** 18, 2480–2493

François Paris
French National Institute of Health,
France.

François Paris is Research Director at Inserm, the French National Institute of Health (ORCID n° 0000-0002-0176-7348). He graduated his Ph.D. from Paris Sorbonne University in 1998 and has been recruited as Inserm Researcher in 2002. Since his Master II, he looks for developing expertise in Radiation Biology, working on different scientifical aspects, such as detection of DNA damage and its repair at Curie Institute (Paris, F) and at MCR genomic Instability (Harwell, UK), radiation sensitivity in function of p53 status at CEA (Paris, F) and at Université Laval (Québec, Canada) and sphingolipids' involvement in radiation response at MSKCC (New York, USA). He published 74 manuscripts in high standard journals, such as Science, Cancer Res. JBC, Nature Medicine which have been quoted more than 5400 times. His H factor is 29.

François Paris is actually directing the team PETRI for "Plasticity of the Ecosystem of Tumor after Radiotherapy and Immunotherapy" in the Inserm Cancer-Immunology Research Center at Nantes University. His research is dedicated to decipher the intercommunication between tumor cells and neighboring normal cells from the host during radiation therapy and to transfer these basic radiobiology to clinical opportunities (http://www.crcina.org/recherche/departement-2-onco/equipe-14-endothelium-radiobiology-and-targeting/). Indeed, he has been working for many years to better understand alterations in the vascular and immune microenvironment in response to radiotherapeutic treatments and evaluate their impact in tumor progression, but also tumor relapse. In order to meet those objectives, new technological approaches in cell therapy, metabolomics and phenotypic screening related to genomic expression analyses are being developed and applied to appropriate cell culture, monolayer or bioprint primocultures, organoids and mouse models. Actual main researches are dedicated to better define similarity and discrepancy of acute and late vascular dysfunctions induced by ionizing radiation, including endothelial cell senescence, in modulating the tumor regression and normal tissue toxicity after different hypofractionated radiation therapy schemes. Through this cognitive and translational research studies, he is aiming to limit the contours of those innovative radiotherapy protocols to optimize their clinical development.

Ann Richmond, Ph.D.
Vanderbilt University,
Nashville, TN, USA

Dr. Richmond is Ingram Professor of Pharmacology and Professor of Dermatology at Vanderbilt University. She holds a Senior Research Career Scientist Award with the Department of Veterans Affairs.

Her research has focused on the role of chemokines and their receptors, with a special focus currently on the role of chemokines in the recruitment of anti-tumor and pro-tumor leukocytes into the tumor microenvironment. Currently she is using targeted therapies that enhance the recruitment of CD8+ T effector cells, dendritic cells, and natural killer cells into the tumor to facilitate the response to immune checkpoint inhibitor therapies in malignant melanoma and breast cancer models.

Dr. Richmond received her Ph.D. in developmental biology at Emory University and this was followed by postdoctoral work in the School of Medicine, Emory University. Her postdoctoral work lead to the purification, cloning and characterization MGSA, now known as the chemokine, CXCL1. After continuing these studies as a faculty member at Emory, she moved to Vanderbilt University in 1989 where she has remained for the remainder of her career. She is currently Director of the Program in Cancer Biology, Associate Director of Basic Education for the Vanderbilt-Ingram Cancer Center and has held an Ingram Endowed Professorship since 2005.

Paul Romesser
Memorial Sloan Kettering Institute,
New York, NY, USA.

Dr. Romesser earned a combined BA/MD at Boston University. He studied at the NCI as a Howard-Hughes Medical Institute and National Institutes of Health Research Scholar in the laboratory of Louis Staudt, MD PhD where he focused on candidate oncogenes, identified in a functional genetic screen, as novel therapeutic targets in patients with non-Hodgkin's lymphoma. He completed residency in Radiation Oncology at Memorial Sloan Kettering Cancer Center, where he was Chief Resident. He is currently an Assistant Member of Memorial Sloan Kettering Cancer Center in the Department of Radiation Oncology and the Early Drug Development Service in the Department of Medicine. He is a physician scientist embedded in the laboratory of Scott Lowe, PhD with an interest in therapy induced senescence and the development of radiation sensitizers and mitigators for gastrointestinal cancers. Dr. Romesser is a member of the NRG Oncology colorectal and non-colorectal committees and the NCI Rectal-Anal Task Force. He is involved in industry and NCI sponsored corporative group clinical trials in rectal and anal cancer.

Norman E. "Ned" Sharpless, M.D.
Director, National Cancer Institute,
Bethesda, MD

Norman E. "Ned" Sharpless, M.D., was officially sworn in as the 15th director of the National Cancer Institute (NCI) on October 17, 2017. Prior to his appointment, Dr. Sharpless served as the director of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, a position he held since January 2014.

Dr. Sharpless was a Morehead Scholar at UNC–Chapel Hill and received his undergraduate degree in mathematics. He went on to pursue his medical degree from the UNC School of Medicine, graduating with honors and distinction in 1993. He then completed his internal medicine residency at the Massachusetts General Hospital and a hematology/oncology fellowship at Dana-Farber/Partners Cancer Care, both of Harvard Medical School in Boston. After 2 years on the faculty at Harvard Medical School, he joined the faculty of the UNC School of Medicine in the Departments of Medicine and Genetics in 2002. He became the Welcome Professor of Cancer Research at UNC in 2012.

Dr. Sharpless is a member of the Association of American Physicians and the American Society for Clinical Investigation. He has authored more than 160 original scientific papers, reviews, and book chapters, and is an inventor on 10 patents. He cofounded two clinical-stage biotechnology companies: G1 Therapeutics and Sapere Bio (formerly HealthSpan Diagnostics). He served as Acting Commissioner for Food and Drugs at the US FDA for seven months in 2019, before returning to the NCI Directorship.

Jan Van Deursen
Rochester, MN, USA.

Jan is passionate about basic medical research and its potential to transform human health and treatment of disease. He has a longstanding interest in questions related to cell cycle control and cellular responses to stress. He helped establish the concept that, with aging and development of age-related disease, wasteful transformed cells that cannot divide litter tissues and organs in small numbers and demonstrated that clearance of these so-called “senescent cells” extends both healthspan and lifespan.

During his Ph.D. training, Jan pioneered technologies to knock down the expression of endogenous genes in mice, and these techniques have proven to be particularly useful in uncovering the physiological function of mammalian genes essential to cell division or viability. In applying these technologies to address the longstanding question as to whether aneuploidy is a cause or a consequence of cancer, Jan discovered that BubR1 (an essential mitotic checkpoint protein that ensures faithful chromosome segregation) is causally implicated in cancer, progeria and aging. Studies originating from his desire to understand these mechanisms are credited with providing the first in vivo evidence that p16-positive senescent cells drive aging and age-related disease, thus establishing cellular senescence as a promising target for therapeutic intervention.

Dr. van Deursen holds a B.S. in Biology, M.S. in Molecular Biology, and Ph.D. in Cell Biology from University of Nijmegen. Recently he was the Vita Valley Professor of Senescence at Mayo Clinic, where he chaired the Department of Biochemistry and Molecular Biology and directed research programs in the Center for Biomedical Discovery, the Comprehensive Cancer Center, and the Kogod Center on Aging. He also serves on numerous national and international grant review panels.

Guangrong Zheng
University of FL,
Gainesville, FL, USA.

Dr. Guangrong Zheng is an Associate Professor in the Department of Medicinal Chemistry at the University of Florida. His group is interested in the development of senolytic agents as potential treatments of age-related diseases, ligands for novel E3 ligases, and small-molecule targeted protein degraders. Dr. Zheng received his Ph.D. in Organic Chemistry from Shanghai Institute of Materia Medica and B.S. in Medicinal Chemistry from Fudan University.

Daohong Zhou
University of Florida,
Gainesville, FL, USA.

Dr. Daohong Zhou is a Professor in the Department of Pharmacodynamics at the College of Pharmacy and a Professor in the Department of Radiation Oncology at the College of Medicine, University of Florida (UF) at Gainesville. He serves as the Associate Director for Translation and Drug Development and the Harry E. Innes Endowed Professor of Cancer Research at the UF Health Cancer Center. His research has led to a better understanding of the cellular and molecular mechanisms by which ionizing radiation (IR) and chemotherapy cause normal tissue damage and the discovery of the first potent and broad-spectrum senolytic agent, ABT263-a specific Bcl-2/xl inhibitor, that can selectively kill senescent cells to rejuvenate both prematurely senescent tissue stem cells induced by IR and tissue stem cells in normally aged mice. This discovery may lead to new therapeutics for various age-related diseases and the side effects induced by chemotherapy and IR. More recently, he developed several proteolysis targeting chimeras (PROTACs) that can target Bcl-xl and other proteins of interest for degradation via the ubiquitination and proteasome system. He found that Bcl-xl PROTACs can selectively induce Bcl-xl degradation in senescent cells and various cancer cells but not in platelets, suggesting that Bcl-xl PROTACs have the potential to be developed as a better senolytic and anticancer agent than ABT263 by not causing thrombocytopenia. Using the PROTAC drug development platform, he is developing additional specific antitumor and better senolytic agents.