New Isotope Production Facility at Los Alamos

The newest U.S. isotope production facility was dedicated and commissioned on January 12 at the Department of Energy's (DOE) Los Alamos Neutron Science Center (LANSCE) in New Mexico. When the $23 million state-of-the-art center reaches full-scale operation later this spring, it will enhance the supply of short-lived medical isotopes in the United States. The facility is funded by DOE's Office of Nuclear Energy, Science, and Technology.

Built over the last 5 years, the facility houses a new beam line and equipment needed to direct part of the 100-million-electron-volt proton beam from the existing LANSCE accelerator to a new target station designed exclusively for the production of isotopes. LANSCE delivered the first proton beam to the new unit at 11:34 PM on December 23, 2003. The facility will allow the production of more than 30 different isotopes in significant quantities and provide the flexibility to insert and retrieve targets while the LANSCE accelerator continues to operate in support of research and national security missions. Among the isotopes that will be produced are ^{67}Cu, ^{73}As, ^{68}Ge, and ^{82}Sr.

Department of Energy

NIH Director's Pioneer Award Program

On January 20 the National Institutes of Health (NIH) opened an invitation for nominations for the Director's Pioneer Award Program, part of a series of initiatives known collectively as the NIH Roadmap for Medical Research. To inaugurate this program, NIH will provide up to $500,000 per year for 5 years to individuals who have the potential to "make extraordinary contributions to medical research."

The award will encourage investigators in the biomedical, behavioral and social sciences, physical and chemical sciences, computer sciences, mathematics, and engineering to take on creative, unexplored avenues of research related to the improvement of human health. Although the research may carry uncertain outcomes, the award will provide investigators with the resources and flexibility needed to pursue truly groundbreaking discoveries. "Historically, leaps in knowledge have frequently resulted from exceptional minds willing and able to explore ideas that were considered risky at their inception," said Elias A. Zerhouni, MD, NIH Director. "We're seeking truly visionary thinkers who are able to make those leaps and change the current paradigms of medical research."

In the past, NIH has awarded grants almost exclusively in support of research projects, not individual researchers. The new award will support scientists or thinkers with pioneering ideas and approaches to contemporary challenges in biomedical research. Applicants will have the intellectual freedom to pursue their ideas and follow them in expected or even unexpected directions. The program is not intended to support ongoing research projects or simply expand the funding of investigators who are already well supported.

Given the unique nature of this award, applicants will undergo a rigorous selection process to establish the potential high-impact benefits of their ideas to medical research and their likely abilities to pursue their concepts. Nominations will be accepted from March 1 through midnight (EST) April 1. For additional information or to submit a nomination, visit the NIH Director's Pioneer Award Web site at www.nihroadmap.nih.gov/highrisk/initiatives/pioneer.

National Institutes of Health

NRC Announces New Agency Hearing Web Sites

The Nuclear Regulatory Commission (NRC) announced on January 14 the availability of 2 new Web sites on agency hearings.

The first (www.nrc.gov/what-we-do/regulatory/adjudicatory/part2revisions.html) is designed to help familiarize members of the public with the NRC's new regulations governing the conduct of hearings. As announced in 2003, NRC has amended the regulations to "make them more effective, efficient, and understandable to the public." These revisions became effective on February 13. Included in the new Web site are several user tools providing: (1) answers to frequently asked questions about the revised rules, (2) cross references between corresponding sections of the former and new rules, and (3) a quick reference guide outlining relevant actions and deadlines for various types of hearings. This site also contains copies of former and new regulations.

The second Web site (www.nrc.gov/what-we-do/regulatory/adjudicatory/hearing-license-applications.html) is designed to inform the public of the NRC's receipt of major applications for licensing actions or certifications, preapplications, or notices of intent to file applications, as well as opportunities for the public to request a hearing or to intervene for major applications and regulatory actions.

Nuclear Regulatory Commission

NIH Launches Virtual Career Center Web Site

The National Institutes of Health (NIH) announced on January 22 the launch of a new Virtual Career Center, developed by the intramural Office of Education. It is designed to meet the needs of the NIH community as well as students and professionals in science and medicine, from the college level to postdoctoral level and beyond. The Web site is arranged into 4 major areas of interest for individuals seeking information on careers and employment: exploring career options, continuing education, employment options and opportunities, and the job search process.

"Whether you are at the very beginning, trying to define your interests or translate an academic major into a

career, or in the final stages of negotiating competing job offers, this Web site will put timely, helpful guidance at the tip of your mouse," said Michael M. Gottesman, MD, Deputy Director for Intramural Research.

The Virtual Career Center site has 55 pages and 1,088 links and is designed so that visitors can focus quickly on specific sets of needs. The site also facilitates a quick focus on areas that meet the user's particular interests. The "Exploring Career Options" section enables users to explore their interests through self-assessment mechanisms, to discover careers and pathways, and to learn important career skills such as writing grants and publishing articles.

The "Continuing Your Education" section provides information on admissions, application services, financial aid, loan repayment, grants, fellowships, education survival skills, and medical schools and other professional programs.

Information on conducting employment searches and learning about opportunities available in industry, academia, and government is found in the "Employment Options and Opportunities" section, and a "Job Search Process" section includes important skills to be used for applying, interviewing, and negotiating for a position.

Visit the site at www.training.nih.gov/careers/careercenter/index.html.

National Institutes of Health

First NIH Collaborative International Awards for Brain Disorder Research

The Fogarty International Center (FIC) of the National Institutes of Health (NIH) and 8 NIH partners announced on January 23 a total of 31 new research planning grants to support international collaborations to study brain disorders in developing countries. The current combined financial commitment from FIC and its partners for the first phase of this program is approximately $8.1 million to support 2-year grants.

This new program grew out of the recognition of the global burden of disease posed by mental illness and a variety of conditions affecting brain function. Currently, brain disorders are responsible for 27% of all years lived with disability (YLDs) in developing countries and, with the exception of sub-Saharan Africa, are the leading contributors to YLDs in all regions of the world.

Each of the new projects will assess needs, develop collaborations and resources, carry out feasibility and pilot studies, and put elements in place to create a strong collaborative research project that will contribute to the long-term goal of building sustainable research capacity in neurologic/neurodevelopment impairment. FIC anticipates that at the end of 2 years, an RFA will be issued to solicit applications for research projects, which will be open to all applicants. A list of the U.S. awardees and their institutions, as well as their partners in the countries in which research will be performed, is available at www.fic.nih.gov. Nuclear medicine will play a crucial role in several of the studies.

National Institutes of Health

2002 U.S. Health Care Spending Reached $1.6 Trillion

The Center for Medicare & Medicaid Services (CMS) issued a report on January 8 indicating that in 2002 health care spending in the United States continued to increase at a rate far outpacing the overall economy. The growth rate for health care was 9.3%, compared with 8.5% in 2001, and marked the sixth consecutive year in which health spending grew at an accelerated rate. Total health care spending rose to $1.6 trillion in 2002, up from $1.4 trillion in 2001 and $1.3 trillion in 2000.

Health expenditures per person averaged $5,440 in 2002, up $419 from $5,021 in 2001. Per person spending in 2000 was $4,670. Prescription drugs continued to lead the rise in personal health care expenditures, with a 15.3% rise in 2002, following a 15.9% increase in 2001. Total spending for prescription drugs in 2002 was $162.4 billion, compared with $140.8 billion in 2001.

Hospital spending increased by 9.5% to $486.5 billion in 2002, marking the fourth consecutive year of accelerated growth. CMS noted in its statement that, "The resurgence in hospital spending growth since 2000 followed a period of managed care expansion that dampened growth in inpatient hospital utilization. Recent spending trends reflect growing demands for services, rising compensation, and other input costs as well as the increased ability of hospitals to negotiate higher prices from private payers."

Spending for physician services reached $340 billion in 2002, an increase of 7.7%, a rate of increase that was slower than the growth rate of 8.6% in 2001.

Private payers funded more than half of national health expenditures in 2002, with private health insurance contributing $549.6 billion (35% of the total). Out-of-pocket payments of $212.5 billion accounted for 14% of expenditures and continued to decline as a share of total spending. More than half the increase in out-of-pocket spending for all health services came from increases in spending for prescription drugs. The public sector accounted for the remaining 46% of health payments, with the Medicaid program funding 16% of aggregate spending ($249 billion), nearly equaling the 17% ($267 billion) spent by Medicare.

Centers for Medicare & Medicaid Services

Newsbriefs from the Literature

Diagnosis

Pittsburgh Compound-B PET in Humans

An article describing the first human study of Pittsburgh Compound-B (PIB), a novel amyloid-imaging PET tracer for diagnosis of

Alzheimer's disease, received worldwide attention from the media in January. E-published ahead of print on January 23 in *Annals of Neurology* by researchers from the University of Pittsburgh and Sweden, the study included 9 (3 young [21 years] and 6 older [69.5 ± 11 years]) healthy individuals and 16 patients with diagnosed mild AD. Klunk et al. found that patients with AD typically showed marked retention of PIB in areas of cortex known to contain large amounts of amyloid deposits. PIB retention was increased most in the frontal cortex (1.94-fold) in these patients. Large increases also were observed in parietal (1.71-fold), temporal (1.52-fold), and occipital (1.54-fold) cortices and the striatum (1.76-fold). PIB retention was roughly equal in AD patients and healthy individuals in those areas known to be relatively unaffected by amyloid deposition. Healthy individuals showed low PIB retention in cortical areas, with no significant differences between age groups. PIB retention correlated inversely with cerebral glucose metabolism as assessed with ^{18}F-FDG, most notably in the parietal cortex. The authors concluded that these results suggested, "that PIB imaging with the novel tracer, PIB, can provide quantitative information on amyloid deposits in living subjects." Klunk issued a statement that was widely quoted in the popular media: "We will likely be able to follow the progression of the disease and speed the development of promising new therapies aimed at halting the build-up of amyloid in the brain." PIB has been patented by the University of Pittsburgh and licensed to Amersham.

Annals of Neurology

^{18}F-FCWAY PET and Panic Disorder

Also receiving wide coverage in the media in January was an article in the *Journal of Neuroscience* (2004;24:589–591) by Neumeister et al. from the National Institute of Mental Health (Bethesda, MD) on the potential for PET imaging of serotonin receptor binding in individuals with panic disorder. The study included 16 unmedicated individuals being treated as outpatients for panic disorder (7 of whom also had current diagnoses of a major depressive episode) and 15 matched healthy individuals. Each participant underwent PET imaging with ^{18}F-trans-4-fluoro-*N*-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl]-*N*-(2-pyridyl) cyclohexanecarboxamide (^{18}F-FCWAY), a radioligand for the serotonin type-1A (5-HT[1A]R) receptor, which has been shown in animal models to contribute to chronic anxiety. Participants also underwent MR imaging for anatomic localization and partial volume correction of PET data. Patients with panic disorder were found to have significantly lower volumes of distribution in the anterior cingulate, posterior cingulate, and raphe than healthy individuals. The results indicated that the 5-HT(1A)R receptors were reduced by nearly a third in these areas in individuals with panic disorder. The authors reported that, "These results provide for the first time in vivo evidence for the involvement of 5-HT(1A)Rs in the pathophysiology of panic disorder."

Journal of Neuroscience

PET and Methamphetamine Withdrawal

In a study published in the January issue of the *Archives of General Psychiatry* (2004;61:73–84), London et al. from the University of California at Los Angeles presented compelling evidence that regional cerebral metabolic abnormalities in methamphetamine (MA) withdrawal are similar to those seen in depression and anxiety. The study included 17 MA abusers who had been abstaining for 4–7 days and 18 healthy control subjects. The 2 groups were compared both for self-reported mood and the results of ^{18}F-FDG imaging of glucose metabolism while performing a vigilance task. Significant differences in glucose metabolism were found between the 2 groups. Glucose uptake was lower in the anterior cingulate and insula and higher in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum in MA users. As expected, the MA users reported higher levels of depression and anxiety than healthy individuals. These reports of depressive symptoms covaried positively with relative glucose metabolism in limbic regions, and assessments of state and trait anxiety covaried negatively with relative activity in the anterior cingulate cortex and left insula. Trait anxiety also covaried negatively with relative activity in the orbitofrontal cortex and positively with amygdala activity. The authors concluded that, "Relationships between relative glucose metabolism in limbic and paralimbic regions and self-reports of depression and anxiety in MA abusers suggest that these regions are involved in affective dysregulation and may be an important target of intervention for MA dependence."

Archives of General Psychiatry

AMT PET in Decision to Reoperate in Epilepsy

Juhasz and a consortium of investigators from Michigan reported in the February issue of *Epilepsia* (2004;45:124–130) on a study to determine whether PET can assist in identifying nonresected epileptic regions in individuals in whom previous cortical resection has failed. The study included 33 patients (ages, 3–26 years) with intractable epilepsy of neocortical origin. Each patient underwent α-^{11}C-methyl-L-tryptophan (AMT) PET imaging 6 days to 7 years after initial surgery and received additional presurgical evaluation for reoperation. Areas with increased AMT uptake were identified and correlated with ictal electroencephalography (EEG) data and a range of clinical variables. Increased cortical uptake of AMT was observed on the side of previous resection in 12 individuals. Timing of imaging

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after surgery was an important factor. Diffuse hemispheric increases were observed in 2 patients imaged within 1 week of surgery, but these increases were not localized. In 10 (43%) of 23 patients who were scanned during a period from 2 months to 2.3 years after surgery, focal cortical increases were observed, and these corresponded to seizure onset on ictal EEG. All patients with localizing AMT PET who underwent reoperation became seizure free or showed significant decreases in seizure frequency. The authors concluded that "AMT PET can identify nonresected epileptic cortex in patients with a previously failed neocortical epilepsy surgery and, with proper timing for the scan, can assist in planning reoperation."

Epilepsia

^{18}F-FDG Predicts β-Blocker Response

In a study published in the January 21 issue of the *Journal of the American College of Cardiology* (2004;43:224–233), Hasegawa et al. from the Osaka University Graduate School of Medicine (Japan) reported on a study to assess whether ^{18}F-FDG PET imaging can predict the response of idiopathic dilated cardiomyopathy (DCM) patients to β-blockers. The study included 22 patients with DCM and reduced left ventricular (LV) systolic function who underwent ^{18}F-FDG PET imaging when fasting and after glucose loading. After administration of a β-blocker, LV function was monitored by echocardiography. Additional histologic data were obtained when 18 patients underwent endomyocardial biopsy. Uptake in the LV after glucose loading was evaluated as average global uptake as a percentage of injected dose (%ID). The authors found that the effectiveness of β-blocker administration corresponded to %ID. The medication was effective in the majority of patients whose %ID after glucose loading was >0.7%, and the sensitivity and specificity of this measure as a predictor of β-blocker efficacy were 83.3% and 90.0%, respectively. Histologic outcomes correlated with predictions based on PET findings. The authors concluded that, "^{18}F-FDG PET is a good predictor for the effectiveness of β-blockers."

Journal of the American College of Cardiology

An Alternative to MIBG for Adrenomedullary PET

In the January–February issue of *Bioconjugate Chemistry* (2004;15:104–111), Lee et al. from Inha University (Inchon, Korea) and Sungkyunkwan University School of Medicine (Seoul, Korea) reported on the development of no-carrier-added m-(ω-^{18}F-fluoroalkyl)benzylguanidines as radiopharmaceuticals for adrenomedullary PET imaging. The compounds were shown to have high radiochemical purity (>97%) and were stable (>90%) in an in vitro metabolic stability assay. Binding to SK-N-SH human neuroblastoma cells was found to be temperature dependent, and binding levels at 4°C were reduced to half those at 37°C, similar to the reduction rate for ^{123}I-MIBG. Additional tissue distribution studies in mice showed the highest uptake in the adrenals and relatively high uptake in myocardium. The authors concluded that, "The results suggest that this radiotracer holds promise as a useful adrenomedullary radiopharmaceutical for PET imaging."

Bioconjugate Chemistry

Early Follow-Up PET in Advanced Head and Neck Carcinoma

Goerres et al. from University Hospital Zurich (Switzerland) reported in the January issue of the *Archives of Otolaryngology–Head &Neck Surgery* (2004;130:105–109) on a study assessing the clinical effect of early follow-up PET in patients with advanced-stage head and neck squamous cell carcinoma (HNSCC).The study included 26 patients with histologically confirmed stage III or IV HNSCC who underwent PET before and 6 weeks after the end of radiation and chemotherapy. PET findings were compared with histologic analyses and 6-month clinical follow-ups. The authors found that PET correctly identified residual tumor tissue, distant metastases, or a second primary tumor in 10 patients, 5 of whom had no clinical evidence of such findings. The results were true-negative in 14 of the remaining cases, false-positive in 1, and false-negative in 1. Sensitivity and specificity for the early follow-up PET scans were 90.9% and 93.3%, respectively. The authors concluded that "whole-body PET scanning approximately 6 weeks after completion of a combined treatment regimen with radiation and chemotherapy can reliably identify locoregional residual cancer and distant metastases or secondary tumors in patients with advanced-stage HNSCC and has a direct influence on management decisions."

Archives of Otolaryngology—Head & Neck Surgery

PET Imaging of Antidepressant Action

A report on a possible suitable radioligand for imaging the action of antidepressant drugs was e-published ahead of print on January 15 in *Psychopharmacology (Berlin).* Marthi et al. from Aarhus University Hospital (Denmark) investigated the regional central biodistribution and pharmacokinetics of *N*-methyl-^{11}C-mirtazapine administered intravenously to 5 healthy volunteers. The compound entered the brain readily, with initial clearance from blood to tissue ranging from 0.31 mL/mL/min in amygdala to 0.54 mL/mL/min in thalamus. The rate of metabolism in the bloodstream was relatively slow, with 20%–40% of activity still present as parent compound at 60 minutes after injection. The volume of distribution was markedly greater in hippocampus and amygdala than in cerebellum, with intermediate levels in the thalamus. The authors noted that

they "envision *N*-methyl-^{11}C-mirtazapine as a molecular probe for PET imaging of antidepressant actions" at sites such as α(2)-adrenoceptors in the living human brain.

Psychopharmacology (Berlin)

^{18}F-FDG PET in Axillary Nodal Staging

Results of a multicenter study of the accuracy of ^{18}F-FDG PET in detecting axillary nodal metastases in women with primary breast cancer appeared in the January 15 issue of the *Journal of Clinical Oncology* (2004;22:277–285). Wahl and colleagues from the PET Study Group reported on 360 women with newly diagnosed invasive breast cancer who underwent ^{18}F-FDG PET imaging. The images were interpreted by 3 experienced readers who were blinded to patient histories, and results from 308 assessable axillae were compared with axillary node pathology. The authors found that ^{18}F-FDG PET had moderate accuracy in detecting axillary metastasis but often failed to detect axillae with small and few nodal metastases. When at least 1 probably or definitely abnormal axillary focus was considered positive, the mean sensitivity, specificity, and positive and negative predictive values for PET were 61%, 80%, 62%, and 79%, respectively. False-negative axillae on PET had significantly smaller and fewer tumor-positive lymph nodes than true-positive axillae. Semiquantitative analysis of axillary ^{18}F-FDG uptake showed that a nodal standardized uptake value >1.8 had a positive predictive value of 90% but a low sensitivity of 32%. Identification of 2 or more intense foci of tracer uptake in the axilla was highly predictive of axillary metastasis (78%–83% positive predictive value) but also had low sensitivity (27%). The authors concluded that, "Although highly predictive for nodal tumor involvement when multiple intense foci of tracer uptake are identified, FDG PET is not routinely recommended for axillary staging of patients with newly diagnosed breast cancer."

Journal of Clinical Oncology

Binodenoson for MPI Pharmacologic Stress

In an article e-published on January 20 ahead of print in *Circulation*, Udelson et al. from the Tufts-New England Medical Center (Boston, MA) reported on a multicenter study of the selective adenosine A2A receptor agonist binodenoson for pharmacologic stress in myocardial perfusion imaging (MPI). The study included 240 patients who underwent SPECT imaging after pharmacologic stress with adenosine and again after pharmacologic stress with binodenoson, using 1 of 4 dosing regimens. Very good to excellent agreement was found between the 2 agents in the extent and severity of reversible perfusion defects. The risk of events and side effects was significantly lower with any dose of binodenoson than with adenosine, as a result of dose-related reduction in subjective side effects (objective events were infrequent). Reduction in the severity of chest pain, dyspnea, and flushing was noted with binodenoson compared with adenosine. The authors concluded that "the selective adenosine A2A receptor agonist binodenoson results in an extent and severity of reversible perfusion defects on SPECT imaging similar to nonselective adenosine receptor stimulation, accompanied by a dose-related reduction in the incidence and severity of side effects."

Circulation

Therapy

Optimal Dose for Recombinant Human Endostatin in Primary Tumor

Davis et al. from the University of Texas M.D. Anderson Cancer Center and the University of Texas–Houston Health Science Center reported in the January 1 issue of *Clinical Cancer Research* (2004;10:33–42) on biomarker analyses designed to correlate changes in refractory solid tumor biology with dose of recombinant human endostatin. The authors had previously reported (*J Clin Oncol.* 2002;20:3804–3814) on a phase I dose-finding study of recombinant human endostatin in 25 patients with refractory solid tumors, in which PET data suggested measurable effects on tumor metabolism. The current study quantified biomarker levels in whole-tissue sections, apoptosis in tumor cells and tumor-associated endothelial cells, microvessel densities, and hypoxia-inducible factor 1α using excisional tumor biopsies obtained from these patients at baseline and after 56 days of endostatin therapy. The authors found significant increases in endothelial death and decreases in tumor microvessel density, with maximum endostatin effects at doses of 249 mg/m^2 and 257 mg/m^2, respectively. Levels of tumor cell death were uniformly low and did not correlate with dose. The authors suggested that endostatin's failure to induce high levels of tumor cell death might explain the lack of significant clinical activity in the phase I trial.

Clinical Cancer Research

Reducing ^{131}I Exposure in End-Stage Renal Disease

In a report published in the January–February issue of *Seminars in Dialysis* (2004;17:53–56), Sinsakul and Ali from Rush University Medical Center (Chicago, IL) addressed the risk of prolonged radiation exposure from renal excretion during ^{131}I therapy in patients with end-stage renal disease. The report included 2 individuals with end-stage renal disease treated successfully for thyroid carcinoma while undergoing chronic hemodialysis. The authors found that single dialysis treatments of 3 and 4 hours performed approximately 20 hours after ^{131}I administration resulted in 80% and 70% reductions in total body radiation levels in the 2

patients. ^{131}I levels were accurately measured with a Geiger-Muller counter during dialysis, and readings showed levels <3 mR/hour, sufficiently low to allow discharge from the hospital. Subsequent monitoring showed no residual radiation contamination of the dialysis machine or exposure to the dialysis staff. The authors concluded that "HD is a critical aspect in the treatment of patients with ESRD receiving ^{131}I and can safely be administered with close planning between the HD staff and the staff of radiation safety."

Seminars in Dialysis

RIT of Prostate Cancer Using PSMA-Specific mAbs

Vallabhajosula et al. from the Weill Medical College of Cornell University reported in the February issue of *Prostate* (2004;58:145–155) on a preclinical study of the effects of ^{131}I-huJ591 and ^{90}Y-1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA)-huJ591 monoclonal antibodies (mAbs) in nude mice bearing LNCaP xenografts. Radiolabeled J591 mAbs have been shown to bind with high affinity to an extracellular epitope of PSMA and localize specifically in prostate-specific membrane antigen–positive LNCaP tumors in vivo. After a single dose of ^{131}I-huJ591 (range, 3.7–11.1 MBq) or ^{90}Y-DOTA-huJ591 (range, 3.7–7.4 MBq), the researchers found a 15%–90% reduction in mean tumor volume, and median survival increased to 2–3 times that of untreated controls. ^{90}Y-DOTA-huJ591 administered in multiple fractionated doses was even more effective, and minimal toxicity was noted. Radiation dose to blood and tumor was higher with the ^{90}Y- than with the ^{131}I-labeled compound. The dose to the tumor at maximum tolerated dose was 2,753 cGy for ^{90}Y-DOTA-huJ591. The authors concluded that, "In nude mice bearing PSMA-positive tumors, radiation dose to the tumor with ^{90}Y-DOTA-J591 is greater for large tumors than with ^{131}I-J591." They suggested that ^{90}Y-DOTA-huJ591 may be a suitable radiopharmaceutical for the treatment of prostate cancer.

Prostate

p53 Expression and RIT and Chemotherapy

In a study published in the January 10 issue of the *International Journal of Cancer* (2004;108:293–300), Blumenthal et al. from the Garden State Cancer Center (Belleville, NJ) reported on efforts to developing multimodal radioimmunotherapies (RIT) and chemotherapies tailored to specific gene expressions in cancer. The study evaluated the effects of the expression of a single gene, the p53 tumor suppressor (which regulates cell cycle arrest to allow for DNA repair after induction of apoptosis in therapy) on the choice of RIT and chemotherapy agents, as well as sequencing and spacing of these agents. The authors established 3 stable p53 transfectants of the SKOV-3 p53null parental line (p53[wt], p53[143mut], or p53[273mut]) and measured dose-dependent growth inhibition from single-modality chemotherapy (doxorubicin, carboplatin, paclitaxel, or topotecan) or radioimmunotherapy (^{90}Y-RS-7 IgG anti-EGP1). Varied sequences of the first and second modality of treatment and spacing between treatments were also performed to determine the optimal combinations for the parental SKOV-3 and each of the 3 transfectants. For multimodal treatments, most combinations of RIT and chemotherapy resulted in a 30%–40% growth inhibition and were either additive or moderately antagonistic. The 3 best (>60% growth inhibition) and 3 worst (<25% growth inhibition) combinations were identified and were unique to the parental p53null and to the 3 transfectants. Although some combinations showed clear advantages, others were antagonistic, with the first treatment modality blocking the growth inhibitory effects of the second treatment modality. The authors concluded that, "The form of p53 expressed affects chemosensitivity and radiosensitivity and will influence optimal multimodal therapy with RIT and chemotherapy and the dose schedule (with RIT first or with drug first) when more than 1 agent is used."

International Journal of Cancer