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Auger processes in the 21st century

Roger W. Howell
Division of Radiation Research, Department of Radiology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

Abstract

Purpose—The extreme radiotoxicity of Auger electrons and their exquisite capacity to irradiate specific molecular sites has prompted scientists to extensively investigate their radiobiological effects. Their efforts have been punctuated by quadrennial international symposia that have focused on biophysical aspects of Auger processes. The latest meeting, the 6th International Symposium on Physical, Molecular, Cellular, and Medical Aspects of Auger Processes, was held 5–6 July 2007 at Harvard Medical School in Boston, Massachusetts, USA. This article provides a review of the research in this field that was published during the years 2004–2007, the period that has elapsed since the previous meeting.

Conclusion—The field has advanced considerably. A glimpse of the potential of this unique form of ionizing radiation to contribute to future progress in a variety of fields of study is proffered.

Keywords

Auger emitters; radiation chemistry; radiation physics; DNA damage; radiotherapy; radionuclides

Introduction

When an atom is ionized by removing an electron from an inner atomic shell, the residual atom is in an excited state. Relaxation back to the ground state occurs rapidly via radiative and non-radiative processes. Radiative processes are those involving the emission of characteristic X-rays. Non-radiative processes, often referred to as Auger processes, result in the emission of Auger, Coster-Kronig (CK), and super-CK electrons. These are distinguished by the shells involved with the transition and are often collectively referred to as Auger electrons. These are competitive processes, with radiative processes being more probable for K-shell vacancies and non-radiative processes being more probable for vacancies in the L-shell and above. Thus, creation of an initial inner atomic shell vacancy

Correspondence: Roger W. Howell, PhD, Department of Radiology, MSB F-451, UMDNJ – New Jersey Medical School, 185 S. Orange Avenue, Newark, NJ 07103, USA. Tel: +1 973 972 5067. Fax: +1 973 972 6474. rhowell@umdnj.edu.

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leads to a series of atomic transitions involving the emission of characteristic X-rays and Auger electrons. This phenomenon has been historically referred to as the Auger effect.

Auger processes are induced by a number of mechanisms. The photoelectric effect can be used to create an inner atomic shell vacancy that leads to a subsequent shower of characterisitic X-rays and Auger electrons. This phenomenon was first observed by Pierre Auger when he exposed a cloud chamber to X-rays (Auger 1925). Inner atomic shell vacancies are also created when radionuclides decay by either electron capture or internal conversion. The ensuing shower of emitted Auger electrons was observed by Meitner while studying radioactive decay (Meitner 1923). The emitted electrons have discrete energies; however, due to the stochastic nature of the relaxation process, the numbers and energies of the emitted electrons vary for each initial vacancy created in a given subshell (i.e., K, L_1, L_2, etc.). Most of these Auger electrons have very low energies (~20–500 eV) with ranges (~1–10 nm) in biological matter. As a consequence, biomolecules in the vicinity of the decay are subject to the direct effects of electron irradiation and indirect effects caused by radical species that arise principally from the radiolysis of water (Wright et al. 1990). In addition, the molecule containing the excited atom is also subject to damage caused by charge neutralization (Pomplun and Sutmann 2004).

Biological damage caused by Auger processes that arise from the photoelectric effect and radioactive decay has been a topic of considerable interest in basic radiobiology, radiation safety, diagnostic radiology, and radiation therapy. Radionuclides that decay by electron capture and internal conversion are commonly used in basic research laboratories and in diagnostic nuclear medicine. Examples of these Auger electron emitters include ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, and ^{201}Tl. The keen interest in these radionuclides began when it was observed that Auger electron emitters can be highly radiotoxic when they decay in the vicinity of DNA in the cell nucleus (Ertl et al. 1970, Hofer and Hughes 1971, Bradley et al. 1975, Feinendegen 1975). In fact, some Auger electron emitters can be as radiotoxic as ^{210}Po which emits 5.3 MeV alpha particles (Howell et al. 1990, Rao et al. 1990). Several comprehensive reviews have been published on the biological effects of Auger electron emitters (Sastry and Rao 1984, Sastry 1992, Kassis 2004, Buchegger et al. 2006, Nikjoo et al. 2006). These are an excellent resource for a complete background and analysis of the field.

The extreme radiotoxicity of Auger electron emitters prompted scientists to extensively investigate the radiobiological effects of Auger electron emitters as well as Auger electrons released as a consequence of the photoelectric effect. Their efforts have been punctuated by a series of international meetings that focused on biological aspects of Auger processes. These began with the founding meeting in 1975 that was organized by Ludwig Feinendegen in Jülich, Germany. This meeting was followed by the first in 1987 in Charney Basset, UK (Baverstock and Charton 1988), the second in 1991 in Amherst, USA (Howell et al. 1992), the third in 1995 in Lund, Sweden (*Acta Oncologica* 1996;35[7]), the fourth in 1999 in Lund, Sweden (*Acta Oncologica* 2000;39[6]), and the fifth in 2003 in Melbourne, Australia (*International Journal of Radiation Biology* 2004; 80[11–12]). The proceedings of each of these meetings have been published and are referenced above. The 2nd–5th proceedings contain a review of published work since the prior meeting (Adelstein 1992, Hofer 1996, Hofer 2000, Kassis 2004). The present manuscript continues in this tradition. It provides a review of articles related to biophysical aspects of Auger processes that were published from 2004–2007, excluding articles published in the previous proceedings.

Review of the literature 2004–2007

DNA damage by Auger processes induced by external beams

Perhaps one of the most extensively studied topics concerning biological damage caused by Auger processes has been DNA damage. These studies have been carried out with Auger processes induced by external beams of ionizing radiation as well as with radionuclides that emit Auger electrons. The last four years of research has continued this trend. Fujii et al. (2004) have used 0.538 keV synchrotron ultrasoft X-rays to create inner shell vacancies in oxygen atoms within molecular constituents of DNA including 2-deoxy-D-ribose, thymine, thymidine, and thymidine 5′-monophosphate. Upon irradiation of dry films of the sugar 2-deoxy-D-ribose, a variety of molecular fragments were observed including H^+, CH_x^+, $C_2H_x^+$, CO^+, CH_xO^+, $C_3H_x^+$, $C_2H_2O^+$ and $C_3H_xO^+$ (x = 1, 2 and 3). When compared with the fragment yields from thymine, thymidine, and thymidine-5′-monophosphate, it was concluded that the sugar is more sensitive to the Auger effect than the thymine base.

Photon activation therapy has been under development since it was proposed by Fairchild et al. (1982). This involves using synchrotron radiation to create inner atomic vacancies in elements such as iodine and platinum, thereby utilizing the induced Auger cascades as a means to increase therapeutic effectiveness (Fairchild and Bond 1984, Sech et al. 2000). This concept was recently extended to He^{2+} beams (Usami et al. 2005). Usami et al. (2005) labeled plasmid DNA with terpyridine platinum (PtTC) and irradiated the samples with He^{2+} ions. They found strong correlations of single-strand break (SSB) and double-strand break (DSB) induction with concentration of PtTC, thereby suggesting that Auger cascades in ionized Pt were the key factor in this enhancement of DNA damage. Addition of dimethyl sulfoxide (DMSO) significantly reduced the enhancement. DMSO completely mitigated the enhancement for SSB induction but not for DSB.

DNA damage from Auger electron emitters in plasmid DNA

A topic of considerable importance to the field is to quantify the number of DSB that are produced per decay of radionuclides that emit Auger electrons. DNA damage caused by the Auger electron emitters ^{123}I and ^{125}I were compared by Lobachevsky and Martin (2005). They labeled plasmid DNA with ^{123}I- or ^{125}I-iodoHoechst 33258 and measured the SSB and DSB yields in the absence and presence of the radical scavenger DMSO. In the absence of DMSO, they found 0.62 and 0.82 DSB/decay for ^{123}I and ^{125}I, respectively. In the presence of DMSO, the values were 0.54 and 0.65, respectively. The authors indicate that their similarly high toxicity in terms of DSB/decay suggests that ^{123}I is well suited for therapeutic applications.

Balagurumoorthy et al. (2006) studied the dependence of DSB production by ^{125}I-labeled m-iodo-p-ethoxy Hoechst 33342 (^{125}IEH) on the number of ^{125}I decays per DNA molecule. Early studies wherein the ^{125}IEH:DNA ratio was 42:1 indicated that ^{125}IEH causes ~1 DSB/decay (Kassis et al. 1999). However, their recent studies with an ^{125}IEH:DNA ratio of 3:1 indicate that the previous experiments overestimated the DSB yield because additional decays in nicked DNA (the high probability of which arises as a consequence of the large number of decays per plasmid) could convert this form into the linearized form. Their analysis of their recent experiments with fewer decays per plasmid has led them to revise their DSB estimate for ^{125}IEH to ~ 0.5 DSB/decay.

Elmroth and Stenerlow (2005) have used pulsed field gel electrophoresis and DNA fragment analysis to measure DSB produced by ^{125}I-labeled 5-iodo-2′-deoxyuridine (^{125}IdU) that was incorporated into the DNA of V79 cells. Cells were loaded with ^{125}IdU and frozen in 10% DMSO at −70°C. They found that on average, each ^{125}I decay produces one local DSB (within 5 nm). In addition to this ‘primary’ DSB, there is on average around 0.6 DSB

produced, presumably within 1 Mbp from the primary DSB. Thus, a total of about 1.6 DSB are produced per decay. In contrast, when the conventional fraction of activity released (FAR) assay was used, only about 1 DSB per decay was measured. Even higher DSB are anticipated under physiological conditions.

Investigation continues on finding compounds that are able to direct Auger electron emitters to the DNA for therapeutic use. It has recently been shown that the aminoacridine compound N-(3-(acridine-9-ylamino)-propyl)-3-iodobenzamide (A3), labeled with ^{125}I, binds to DNA and causes about 1–1.4 DSB/decay (Kullberg et al. 2005). Accordingly, this radiochemical has therapeutic promise provided that a pharmaceutical can be identified to deliver and internalize this agent specifically within tumor cells.

Theoretical models to study plasmid DNA damage caused by Auger electrons continue to evolve to levels of increasing sophistication. Lobachevsky et al. (2004) have created a semi-empirical model to analyze plasmids following the decay of ^{125}I on plasmid DNA. Their model accounts for various possibilities of creating linearized, relaxed, and supercoiled plasmids in the absence and presence of the radical scavenger DMSO. Among the possibilities are a single SSB, single DSB, or two SSB created by a single decay on a plasmid, and single SSB and DSB created by two decays on the same plasmid. Their model provided an excellent fit to the experimental data (i.e., SSB and DSB per decay) thereby affording a more comprehensive understanding of the DNA damage caused by Auger electron emitters. Kümmerle and Pomplun (2005) have taken a different approach and designed a new computer generated model of pUC19 plasmid DNA. This model can simulate the various conformations that the plasmid can undergo depending on the experimental conditions. To facilitate simulation of DNA-damage caused by Auger electrons, it has been designed to interface with Monte Carlo radiation track structure codes. With this model, Edel et al. (2006) have carried out a computer simulation of damage caused by ^{125}I in plasmid DNA in the absence and presence of scavenging with DMSO. Their model shows that radiotoxicity of Auger electrons from ^{125}I decay in plasmid DNA is caused mainly by direct mechanisms (92% of linearization events (LE) arises from direct hits). In contrast, indirect mechanisms were predominant when ^{125}I is freely distributed (> 87% of LE are scavengable). Good agreement was observed between the theoretical data and recent experimental findings. This indicates that their modifications including new target, new sampling algorithms, and new electron cross sections have substantially improved their capacity to simulate experimental observations.

The nature of the DNA damage caused by ^{125}I decays has recently been studied by producing site-specific radiation-induced DSB in plasmid DNA by triplex forming oligonucleotide (TFO) targeted ^{125}I (Datta et al. 2005a, 2005b, 2006). This approach enables precise delivery of ^{125}I to a specific predetermined location on the DNA. In these studies, base damage around the site of decay was assessed on the fragments containing the 3′ and 5′ ends of the upper and lower strands. This novel approach precisely elucidated base damage clustering within eight bases of the targeted site. This damage was mitigated to some extent by the presence of DMSO. Interestingly, base damage also occurred >24 bp from the decay site. The authors hypothesize that this may be caused by a charge migration mechanism. Baverstock's soliton theory also comes to mind where it was proposed that the energy deposited in DNA by ionizing radiation can be transmitted over long distances along the molecule (Baverstock and Cundall 1988).

Interpretation of damage caused by multiple ^{125}I decays in TFO requires theoretical models of increasing complexity. Nikjoo et al. (2006) have developed a theoretical TFO model consisting of linked 10mers and three ^{125}I decay sites. A total of 18,000 decays were simulated and the frequency distribution of strand breaks was recorded. The SSB

distributions around each decay site were symmetric and similar in magnitude. A highly sophisticated model has also been developed by Li and colleagues (Li et al. 2004, Li 2006) to simulate ^{125}I induced DNA fragmentation in DNA-protein and 41-mer synthetic oligodeoxynucleotide (oligoDNA). Radiation transport was simulated with PARTRAC and damage to DNA caused by direct (not scavengable) and indirect (scavengable) effects was studied. Direct effects included those due to direct interaction of the emitted radiations with the molecules, as well as those due to the charge neutralization processes associated with the Auger cascade process. With their inherent assumptions, the neutralization process was found to be primarily responsible for the damage caused within 5–7 base pairs of the decay site. This approach yielded good agreement between experimental data in the literature and their calculations.

Auger emitters as probes of molecular structure

Recently Auger electron emitters have been used as probes to ascertain important molecular structures. He et al. (2004b) have used ^{125}I to label oligonucleotides that contained four human telomeric repeats at a single internal position. The labeled oligos were then placed in different ionic conditions, allowed to fold into quadruplexes, and then frozen for decay accumulation. The probabilities of breaks at individual nucleotides were determined by sequencing gel electrophoresis. They then analyzed the quadruplex fold based on the comparison of the probability of breaks with the distance from ^{125}I to the corresponding nucleotides derived from the available nuclear magnetic resonance (NMR) and X-ray quadruplex structures. Interestingly, their data suggest that an antiparallel molecular conformation was present when both K^+ and Na^+ were present. However, Na^+-containing solution favored the basket-type antiparallel quadruplex and K^+ favored the chair-type antiparallel quadruplex. Based on these data, it appears that antiparallel and parallel conformations coexist in solution and ion concentration determines which configuration is favored. This study attests to the unusual capacity of Auger electron emitters to elucidate important biological structures at the molecular level. This is likely to be an important use of Auger emitters as we continue with our work in this 21st century (Laughton et al. 2004, Nikjoo et al. 2006).

The experimental DNA damage data that arise from Auger processes are complex indeed. Theoretical modeling plays a key role in interpreting these data and outstanding progress has been made. The present generation of theoretical modeling of DNA damage caused by Auger processes is the result of an evolution that has occurred over more than 20 years. New capabilities in the realm of biological assays, such as those of Datta et al. (2005a, 2005b, 2006), will require that the models continue to evolve. Among the many aspects that are considered by the modelers are the stochastics of the number of decays per plasmid, electron cross sections for low energy electrons in water and in DNA, stochastics of the Auger electron spectra, direct effects of the electrons, indirect effects of radical species produced via radiolysis of water, charge transfer, charge neutralization, and the effect of molecular structure on all of the above. This list is by no means exhaustive. These models rely on the accuracy and completeness of the data that are put into them. Accordingly, it is essential that the latest discoveries in radiation physics and chemistry be incorporated into the models. The last four years have been productive and many new discoveries and technologies have emerged that are of importance to modeling Auger processes. Further evolution of our DNA damage models will likely take advantage of these new findings. These will be reviewed in the next subsection of this article.

Physics of Auger cascades

To facilitate calculation of the radiation absorbed dose, experimental investigations with radioactive materials necessarily require accurate determination of activity. Counting

efficiencies are necessary for quantifying activity of radionuclides that decay by electron capture or internal conversion. When using liquid scintillation techniques, LMM Auger electron energies are an important aspect of this determination (Malonda et al. 2006). Malonda et al. (2006) have calculated mean LMM Auger electron energies and counting efficiencies for the Auger electron emitters ^{55}Fe and ^{125}I.

Emfietzglou and Nikjoo (2005) have studied the impact of various model approximations on inelastic low-energy electron cross sections for liquid water which are critical for Monte Carlo simulation of Auger electron track structure and radiation absorbed dose estimates in small volumes. They examined the influence of the optical data set, the dispersion algorithm, and the perturbation and exchange Born corrections. They found that the shape and position of the energy loss spectrum remains essentially unchanged, however, peak height is influenced up to a factor of 1.5. Larger discrepancies were observed for electron energies below 100 eV. These findings prompted them to calculate new inelastic cross sections for electrons in the energy range 0.1–10 keV with accuracies ~5%, comparable to higher energy electrons (Emfietzoglou and Nikjoo 2007). New ionization cross sections for the interaction of low energy electrons with DNA bases and sugars, and amino acids, have been developed by Peudon et al. (2006). Rather than relying on common methods that use extrapolations based on cross-sections for liquid water, their approach implements the binary-encounter dipole (BED) model. Their electron cross-sections for DNA are in good agreement with published values, and the amino acid results have not been reported on previously. Overall, these developments in cross sections for low energy electrons will play an important role in furthering our understanding of the biological effects of Auger electron emitters.

As interest in Auger electron emitters moves forward, there is continued need for knowledge of the spectrum of Auger electrons emitted by radionuclides. Given the biophysical importance of the very low energy Auger electrons, and the inherent difficulty in measuring their yields, theoretical calculation of Auger electron spectra has traditionally been the source of such data (Kassis et al. 1980, Charlton and Booz 1981, Rao et al. 1983, Pomplun et al. 1987, Howell 1992). Nikjoo et al. (2006) have recently estimated the Auger electron yields for ^{124}I. Bé et al. (2006) have calculated highly detailed K- and L- Auger electron spectra for several radionuclides and found that their averaged values are in good agreement with values published in the literature. Both deterministic and Monte Carlo approaches have been used to calculate Auger electron spectra. The advantage of the Monte Carlo approach is that it provides information regarding the stochastics of the decay process, namely the spectrum for each individual decay. Recently, Carles and Malonda (2006) have devised a new deterministic approach that is capable of providing some detail regarding Auger spectra for individual decays. Yakushev et al. (2005) have measured the K and L Auger electron spectra of ^{140}Nd and ^{111}In. To compare their relative potential for therapeutic applications of Auger electron emitters, they determined ratios of Auger electron yields per decay. They found that ^{111}In emitted more K- and L-shell Auger electrons than ^{140}Nd; however, ^{140}Nd emitted substantially more low energy L-shell Auger electrons (2.8–7 keV). Their findings were in good agreement with theoretical calculations.

Theoretical simulations of Auger electron spectra, and the ensuing interaction of Auger electrons with water, DNA, and other molecules of importance to biological processes, rely on the input data used to create the simulations. A number of recent developments in atomic physics are of importance to these simulations. The studies described in the remainder of this subsection review these important developments.

Takahashi et al. (2006) have developed a new approach for calculating Auger decay transition rates that include the effects of core-hole excited state dynamics. Their approach

was tested for normal and first resonant Auger processes in gas-phase water. Interestingly, the Auger decay of OH and O fragments that arise as a consequence of ultrafast dissociation of H_2O, contributes to the total intensity. This component is of increasing importance with increasing excitation energy. With the exception of the Franck-Condon vibrational structure, their calculated Auger spectra are a close match to experimental data. Ohrwäll et al. (2005) have studied the Auger electron spectrum that arises following core ionization of liquid water clusters. The resulting Auger electron spectrum falls between those observed in the gaseous and solid phases and is characterized by broadened energy bands and a shoulder at the high energy region of the spectrum. This shoulder appears to be due to delocalized final states in which the two valence holes are mostly located at different water molecules. These studies prompt thought on the potential importance of Auger electrons emitted by ionized water molecules in the first layer of water around the DNA.

Feyer et al. (2005) have studied Auger spectra following ionization of CO and CO_2. It has been shown that that proper consideration of the vibrational broadening and shift of the bands due to the dynamics of the nuclei is needed to accurately calculate the resulting Auger spectra. These findings confirm that typical calculation of Auger spectra based on vertical electronic transition energies and neglect of vibrational effects can lead to inaccuracies. This becomes more and more important as dicationic states of higher binding energies are considered. There are also many other studies that are of importance to modeling the Auger cascade process (Kato et al. 2004, Kou et al. 2004, Kugeler et al. 2004, Tanis et al. 2004, Viefhaus et al. 2004, Villani and Tarantelli 2004, Kawai 2005, Kawai et al. 2005, Hikosaka et al. 2006, Melero Garcia et al. 2006, Hikosaka et al. 2007).

Cederbaum et al. (1997) identified a new atomic de-excitation process called interatomic coulombic decay (ICD). This is distinct from Auger processes and is a competing process. When an inner atomic shell (*core*) vacancy is created as a consequence of photoionization, the resulting cation is normally found in a highly excited state above the double ionization threshold. A valence electron can fill the core hole liberating enough energy for the emission of a second electron, an Auger electron. The kinetic energy of the Auger electron is largely independent of the energy of the incident radiation and depends primarily on the intra-atomic electronic structure. The Auger electron spectrum is not significantly dependent on the chemical environment. In contrast, an ionization from the inner-*valence* region (~20–80 eV) leads to cationic final states below the double ionization threshold and an autoionization process on the same site is often inhibited. If the charge of a possible dication is delocalized, as it could be in a cluster, then the yielded excess energy obtained by filling the inner valence hole now is sufficient to ionize a valence electron on a *neighboring* site resulting in a two-site doubly-ionized system. This process is known as interatomic or intermolecular Coulombic decay. ICD has been shown to be a common decay mechanism in hydrogen bonded clusters as well as in van der Waals clusters (Cederbaum et al. 1997). Pernpointer et al. recently showed that inclusion of ICD has a substantial effect on Auger spectra that arise following the creation of vacancies in iodine atoms located within molecular structures (Pernpointner and Knecht 2005, Pernpointner et al. 2006). A further process called resonant ICD, analogous to resonant Auger decay, has also been demonstrated by Barth et al. (2005). Thus, it is safe to say that in the molecular environment, ICD processes compete with Auger decay. The current models used to calculate the yields and energies of Auger electrons do not consider ICD. However, it is not clear at present what significance the role that ICD would have on the radiobiological effects that result as a consequence of inner atomic shell vacancies created by photoionization, electron capture, or internal conversion. Further work is necessary to assess this.

Recent advances in experimental atomic physics have made it possible to observe atomic rearrangements in the attosecond time realm (Kienberger et al. 2004, Uiberacker et al.

2007). Laser technology was used to observe subfemtosecond ionization steps following the creation of atomic vacancies. This approach enables them to probe the transient population of short-lived valence electronic states in excited atoms or molecules. Most importantly, this provides a window into multi-electron dynamics such as Auger processes that occur on an attosecond to femtosecond timescale. Ultimately, these techniques are likely to provide valuable information of importance to biological aspects of Auger processes. These include more accurate transition rates for N- and O-shell transitions, effect of molecular interactions on Auger transition rates, and perhaps the possibility of observing Couloumb explosion in real time.

Cellular responses to Auger processes

In view of the extreme radiotoxicity of Auger electron emitters, there has been concern regarding the risk of using these radionuclides in diagnostic radiopharmaceuticals. While this debate has been quite active in the past as evidenced by numerous publications on this topic, relatively few articles were published on this topic over the last four years. The Auger electron emitter ^{99m}Tc is the most widely used Auger electron emitter in nuclear medicine. Kriehuber et al. (2004a) have exposed cultured SCLII cells to ^{99m}Tc-pertechnetate and assayed cell killing (colony forming assay), DNA damage (micronuclei), and apoptosis. Cellullar uptake was low and results for the cell killing and micronucleus end points indicate that ^{99m}Tc-pertechnetate is substantially less radiotoxic than acute ^{60}Co γ-rays (relative biological effectiveness (RBE) <1). This finding is in general agreement with those of Narra et al. (1994). Accordingly, the authors argue that the current risk estimates for ^{99m}Tc-pertechnetate are adequate and do not require reassessment. The computational modeling of Pomplun et al. arrived at a radiation weighting factor of 1.2 for ^{99m}Tc, a value in good agreement with the above data (Pomplun et al. 2006). Kriehuber et al. (2004b) did, however, find that ^{99m}Tc-pertechnetate appears to be more effective in causing apoptosis. This finding will be further investigated. In contrast to the results for ^{99m}Tc, Kriehuber et al. have used the same experimental system to show that ^{65}Zn is considerably more radiotoxic than acute ^{60}Co γ-rays. RBE values of 4, 2, and 5–8 have been found for cell killing, micronucleus formation, and apopotosis. The high radiotoxicity of this Auger electron emitter may be attributed to enhanced amounts of Zn^{2+} in the perinuclear region of the cells suggesting a major energy deposition close to the nuclear envelope.

Health risks associated with testicular exposure to diagnostic radiopharmaceuticals have historically been the subject of intense study (Hosain et al. 1978, Gupta et al. 1981, Rao et al. 1995). The high RBE of these radiochemicals in testis was demonstrated in rodents (Rao et al. 1983, 1988). Nettleton et al. (2004) recently administered ^{111}InCl or ^{201}TlCl to volunteers that were undergoing scheduled orchidectomies and, upon their surgical removal, quantified the testicular uptake of these radiopharmaceuticals. Measurements indicate that ICRP dose estimates for ^{111}InCl and ^{201}TlCl are under- and overestimated by a factor of about 4, respectively. As in the mouse studies (Rao et al. 1983, 1988), both radiochemicals gain access to the human seminiferous tubules (Nettleton et al. 2004). However, cellular uptake was not measured specifically. Nevertheless, their study provides valuable data for estimating the absorbed dose to human testes from ^{111}In and ^{201}Tl that should be taken into account in risk estimation.

Radioiodinated Hoechst-33342 has been used extensively to localize ^{125}I in the DNA of the cell nucleus, a location generally considered to be required to realize the maximum toxicity imparted by a given Auger electron emitter. Yasui et al. have shown that cells labeled with ^{125}I-H33342 are killed in a dose-dependent manner consistent with a monoexponential function (Yasui et al. 2007). The mean lethal number of ^{125}I decays per cell was 122 and a linear increase in DNA DSB induction was observed that was equivalent to 15 γ-H2AX foci/cell (Yasui et al. 2007).

Flow cytometric analysis has shown that induction of γ-H2AX correlates with targeting of the nuclear genome with ^{125}I-labeled triplex forming oligodeoxynucleotides (TFO) (Panyutin et al. 2005). Thus, γ-H2AX can be used as a sensitive indicator of targeting in order to rapidly screen a large number of ^{125}I-TFOs for potential application in gene therapy. Screening is essential to find optimal combinations of Auger electron emitters and TFO that will increase damage to the target region of the DNA and decrease DNA damage from non-specific irradiation (Panyutin and Neumann 2005). It stands to reason that the same approach could be adopted for other Auger electron emitting radiochemicals as well.

Urashima et al. (2006) have studied radiation-induced apoptosis caused by DNA-incorporated ^{125}IdU in several human tumor cell lines. They found that apoptosis initiated by ^{125}IdU depends on dose, correlates with cell radiosensitivity and takes place through a caspase-3 (CASP-3)-mediated pathway. In contrast, γ-irradiation induced apoptosis does not correlate with cell radiosensitivity and appears to occur through a CASP-3-independent pathway and/or a CASP-3-mediated pathway. Thus, ^{125}I-induced apoptosis appears to behave differently than for conventional radiations. Differences in cellular responses following irradiation with γ-rays and ^{125}I have also been observed in gene expression studies. Sokolov et al. (2006) compared genome-wide responses in IMR-90 human lung fibroblasts following irradiation with high- and low-dose rate γ-rays and ^{125}IdU. They found that greater than 2000 genes were up- or down-regulated in the case of high- and low-dose rate γ-rays. In contrast, only 206 genes were altered in the case of ^{125}IdU. Furthermore, there was considerable overlap between changes in gene expression caused by ^{125}IdU and γ-rays.

An intriguing area of research is the capacity of Auger electron emitters to impart radiation-induced bystander effects. These studies were in their infancy at the time of the last Auger Symposium. Since then, Kishikawa et al. (2006) have studied the capacity of ^{125}I and ^{123}I to impart bystander effects in an *in vivo* tumor model. Specifically, they labeled LS174T cells with either ^{125}IdU or ^{123}IdU, mixed them with either unlabeled cells or lethally irradiated cells, and injected them subcutaneously into nude mice. Tumor size was monitored and it was found that ^{125}IdU caused inhibition of tumor growth whereas ^{123}IdU promoted tumor growth. The mechanisms underlying this observation were studied using microarray analysis which showed that the cell growth inhibitors TIMP1 (tissue inhibitor of metalloproteinase) and TIMP2 are overexpressed by dying ^{125}I-labeled cells and the tumor-cell mitogen angiogenin is overexpressed by lethally irradiated ^{123}I-labeled cells. Bystander effects caused by incorporated radionuclides have also been examined by Boyd et al. (2006). They transferred cell culture medium from flasks containing cells labeled with ^{125}I-meta iodobenzylguanidine (MIBG), ^{131}I-MIBG, or ^{211}At-meta astatatobenzylguanidine (MABG) to flasks containing unirradiated recipient cells. This culture medium, which contained no significant radioactivity, was found to be toxic to the recipient cells. The cell survival response of the recipient bystander cells was dose dependent in the case of the low linear energy transfer (LET) ^{131}I-MIBG, but was U-shaped for the high-LET type irradiation afforded by ^{125}I and ^{211}At. These studies again point out that Auger emitters can cause biological responses that are quite different in nature than those observed for low-LET radiations.

Finally, the effects of the Auger electron emitter ^{125}I on mitochondrial DNA has been a subject of interest for some time. Using a technique to inhibit mitochondrial uptake of ^{125}IdU, Yasui and Hofer (1986) were able to show that the radiotoxicity of ^{125}IdU was primarily caused by nuclear DNA damage and not mitochondrial DNA damage. This radiochemical localizes predominantly in the nuclear DNA. Given the substantial attention that mitochondrial DNA damage has received of late (Van Houten et al. 2006), it may be of interest to specifically target mitochondria with an Auger electron emitter such as ^{125}I. The

recent studies of VanBrocklin et al. (2007) have shown that one can target them with ^{125}I-iodorotenol or ^{125}I-iodorotenone. These findings suggest that Auger electron emitters could be used as precision radioprobes to study mechanisms related to amplified oxidative stress caused by damage to mitochondrial DNA and its relationship to a variety of diseases.

Therapeutic aspects of Auger processes

Stereotactic radiosurgery plays an important role in radiation oncology. Exploration of the potential to combine stereotactic radiosurgery and photon activation therapy of cancer has recently been studied. Corde et al. (2004) have carried out studies to identify the optimal energy for IdU and contrast agent enhancement of the radiotoxicity of X-rays. They have identified 50 keV as the most effective energy which is considerably above the iodine K-edge of 33.169 keV. Monoenergetic X-rays just above the K-edge were less effective. Accordingly, Adam et al. (2006) stereotactically delivered 50 keV monochromatic X-rays to activate iodine upon its infusion into the carotid artery of glioma tumor bearing rats. They found that the combination of iodine and X-rays substantially improved survival compared to either iodine or X-rays alone. Recent studies indicate that even further enhancement can be achieved using novel approaches to enhance iodine uptake in the tumor (Rousseau et al. 2007). Studies have also carried out using the same approach with a combination of 78 keV monochromatic X-rays and cis-platinum (Biston et al. 2004).

Interest also continues in developing chemo-Auger combination therapy of cancer. This approach implements a chemotherapy agent that is labeled with an Auger electron emitter (Hou et al. 1985, Howell et al. 1986, Azure et al. 1992). Garnuszek (2004) has produced a Pt(II)Cl_2-^{125}I-histamine complex and tested its capacity to inhibit the growth of transplantable colon carcinoma (C38) in mice. It was found that a combination of nonradioactive Pt(II)Cl_2-histamine and Pt(II)Cl_2-^{125}I-histamine was more effective than either alone in inhibiting tumor growth. It is interesting to speculate that radiations emitted by ^{125}I, or ICD processes arising from vacancies in the residual tellurium atom, may be creating L-shell vacancies in Pt which in turn results in a large Auger cascade. Bleomycin, and the DNA-intercalators daunorubicin and dauxorubicin have also been explored for use in chemo-Auger combination therapy of cancer (Ghirmai et al. 2005, Jaaskela-Saari et al. 2005, Ickenstein et al. 2006). Recent studies with ^{125}I-labeled dauxorubicin indicate that the radiopharmaceutical localizes in the cell nucleus and is dramatically more toxic than its unlabeled counterpart (Ickenstein et al. 2006). Finally, Bapat et al. (2005) showed that ^{125}I-labeled bakuchiol, a meroterpine phenol isolated from plants, was cytotoxic when taken up by murine tumor cells and its cytotoxicity is significantly greater than unlabeled bakuchiol. Notably, mouse splenocytes were not adversely affected by ^{125}I-bakuchiol.

There has been considerable interest in using ^{131}I-MIBG for cancer therapy. However, adverse hematological toxicity has limited its use. He et al. have investigated the capacity of ^{123}I-MIBG to kill cultured neuroblastoma cells with its short-range Auger and conversion electrons while sparing cells of haematopoietic lineage (He et al. 2004a). Their findings suggest that ^{123}I-MIBG may be useful for residual small volume and micrometastatic neuroblastoma.

Radiolabeled 5-iodo-2′-deoxyuridine (^{125}IdU) has been repeatedly shown to be highly cytotoxic when localized on the DNA in the cell nucleus. One of the well-known drawbacks of this radiochemical for therapeutic applications is its rapid dehalogenation *in vivo*. Over the past several years, efforts have been taken to explore the alternate thymidine analog 5-iodo-4′-thio-2′-deoxyuridine (ITdU) as a means to deliver ^{123}I or ^{125}I to the DNA of tumor cells (Reske et al. 2007). ITdU was selected for a number of reasons, among them are that it is incorporated into nuclear DNA through the thymidine salvage pathway, it is not incorporated into mitochondrial DNA, and most importantly, its *in vivo* stability is

considerably higher than other 5-halogenosubstituted deoxyuridines. Reske et al. (2007) have recently shown that ^{123}ITdU causes DNA damage and induction of apoptosis in leukemia cell lines that are both sensitive and resistant to β- or γ-irradiation and doxorubicin. Furthermore, like IdU, they were able to metabolically stabilize ^{123}ITdU by inhibiting thymidylate synthase (TS) activity with 5-fluoro-2′-deoxyuridine (FdU) and increase cellular uptake, DNA incorporation, and ^{123}ITc–induced apoptosis. Perillo-Adamer et al. (2006) have also revisited the concept of pretreating cells with fluorodeoxyuridine (FdU) to increase the cytotoxicity of ^{125}IdU. Early studies indicated that while FdU increases mean cellular uptake by about 3-fold, little improvement was observed in the overall killing of the population (Kassis et al. 1991). Perillo-Adamer et al. carried out additional studies with three cell lines and found that a 1-h incubation with 1 μM FdU resulted in ≥7.5-fold increase in ^{125}IdU uptake at 16–24 h later. Cell synchronization in S phase was observed with a peak of ≥69.5% in the same timeframe. This corresponded to a 2.5- to 4.1-fold increase over baseline. These findings suggest that manipulation of the cell-cycle with FdU may increase the therapeutic potency of ^{125}IdU. This strategy has been adopted for increasing tumor uptake of ^{125}IdU following its intratumoral administration (Buchegger et al. 2004). This approach involves pretreating glioblastoma xenograft bearing mice with FdU to block de novo synthesis of deoxythymidine to increase the uptake of ^{125}IdU. Nearly a five-fold increase in retention of the ^{125}IdU was observed in the FdU-treated mice compared to untreated.

Kit formulations are available for the preparation of radiolabeled IdU (Foulon et al. 1995, Schaffland et al. 2004). Semnani et al. (2005) recently showed that the formulation of a SnUdR based kit can be manipulated to maximize uptake of IdU by the tumor. Tumor to non-tumor uptake of ^{123}IdU/^{125}IdU was up to 6- to 7-fold higher than controls depending on the quantity of SnUdR used in the formulation. While clarification of the mechanism(s) involved in this enhancement is needed, it is possible that the SnUdR may be inhibiting/modulating the de novo thymidylate synthetic pathways.

The radionuclide ^{64}Cu decays to either stable ^{64}Ni (β^+ decay, yield = 0.18; or electron capture, yield = 0.45) or to ^{64}Zn (β^- decay, yield = 0.37). Accordingly, a number of Auger electrons are emitted by this radionuclide which has been of considerable interest for targeted radionuclide therapy. Recently, Obata et al. (2005) synthesized ^{64}Cu-diacetyl-bis (N^4-methylthiosemicarbazone) (^{64}Cu-ATSM), a prospective radiotherapy agent for the treatment of hypoxic tumors, and carried out cytotoxicity studies in Lewis lung carcinoma cells. Like ^{124}I, this radionuclide irradiates the cells with Auger electrons, beta particles, and positrons. The radioactivity was distributed in both the cytoplasm and nucleus. About 4500 decays per cell were required to achieve 37% survival (Obata et al. 2005). This is considerably higher than the typical 100 decays required for DNA-incorporated ^{125}I. However, assuming that the diameters of the nucleus and cell are 8 and 10 μm, respectively, and 80% of the intracellular activity is in the cytoplasm, the D_{37} dose to the cell nucleus can be estimated using the cellular S values of Goddu et al. (1997). With these assumptions one obtains D_{37} = 4500 decays (0.8 * 3.17 × 10^{-4} Gy/decay + 0.2 * 1.48 × 10^{-3} Gy/decay) = 2.5 Gy.

Radioimmunotherapy of cancer with antibodies radiolabeled with Auger electron emitters is an evolving approach. In an effort to identify the optimal Auger electron emitter for this purpose, Michel et al. have recently carried out a number of studies (Michel et al. 2004, 2005a, 2005b, 2005c). Cell culture studies were undertaken with monolayers of human carcinoma cells and radiolabeled anti-epidermal growth factor receptor and anti-epithelial glycoprotein-1, conjugated to^{111}In or ^{125}I. Interestingly, their results indicate that the highest degree of cell killing can be obtained with the ^{111}In-labeled antibodies and this is due to the higher specific activity that can be attained in this case. Further studies were

carried out with ^{111}In- or ^{125}I-labeled anti-human epidermal growth factor receptor 2 (HER2) antibodies against breast carcinoma SK-BR-3 and ovarian carcinoma SK-OV-3.ip1 cells. Both showed good cytotoxicity. In vivo studies with anti-cluster of differentiation antigen 74 (CD74), anti-CD20, and anti-human leukocyte antigen (HLA-DR), labeled with the same Auger electron emitters, indicate that these radiopharmaceuticals can successfully treat subcutaneous Raji, Daudi, and RL-B lymphoma human tumors in severe combined immunodeficient mice. However, only disease with size <2 mm in diameter were sterilized indicating that radioimmunotherapy with Auger electron emitters will be useful for micrometastatic disease. Further progress in radioimmunotherapy has also been made in terms of using antibodies to deliver Auger electron emitters to the nucleus of tumor cells. An anti-CD33 monoclonal antibody HuM195 was modified with peptides that contain the nuclear localizing sequence of simian virus 40 large T antigen and labeled with ^{111}In (Chen et al. 2006b). Cell culture and animal studies indicate that the ^{111}In was delivered to the nucleus of the tumor cells thereby indicating that this is a promising approach for treating acute myeloid leukemia (AML). Attainment of nuclear localization is a major step forward in radioimmunotherapy with Auger electron emitters.

A number of somatostatin analogs have been identified as having potential for targeted therapy of cancer. Capello et al. (2005) studied the effect of different administered activities on the therapeutic capacity of ^{111}In-diethylenetriamine pentaacetic acid (DTPA)-octreotide against somatostatin receptor-positive rat pancreatic CA20948 tumours expressing the somatostatin receptor subtype 2 (sst2). They found a strong dependence of therapeutic effect on tumor size with therapy being most effective in animals with tumor volumes <1 cm^3. Interestingly, it was also noted that the treatment upregulated receptor expression on the tumor cells thereby suggesting increased efficacy for repeat treatments. Development of new variants of ^{111}In labeled octreotide for diagnostic and therapeutic applications are also underway. Ginj et al. have designed and characterized new 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-based peptides ^{111}In-DOTA-Nal^3, Thr^8-octreotide and ^{111}In-DOTA-BzThi^3, Thr^8-octreotide (Ginj et al. 2005a, 2005b). The peptides were compared with our clinical gold standard ^{111}In/^{90}Y-DOTATyr^3-octreotide. They show superior pharmacologic properties when compared with with their clinical gold standard ^{111}In/^{90}Y-DOTATyr^3-octreotide. Also studied recently is radiolabeled DOTA-Tyr^3-octreotate (DOTA-TATE). Korde et al. (2007) have iodinated this analog to obtain ^{125}I-DOTA-TATE and determined its biodistribution following intravenous administration in melanoma-bearing C57BL/6 mice. At 24 h post-injection, kidney and tumor activities were 4.7 and 2% injected dose per gram, respectively. This study suggests a role for ^{125}I in targeted therapies with somatostatin analogs. Clinical trials with ^{111}In-DTPA-Phe-Octreotide have been undertaken by Limouris et al. (2005). They selected patients with neuroendocrine liver metastases and administered 4070 to 7030 MBq at each of up to 12 administrations via selective hepatic catheterization. Follow-up was done with computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) with US being identified as the best of the three. Very good tumor response was observed. A pilot clinical trial that used ^{111}In-DTPA-octreotide to treat differentiated thyroid carcinoma was carried out by Stokkel et al. (2004). They found that high doses (7,400 MBq at 2–3 week intervals) of ^{111}In-DTPA-octreotide resulted in stabilization of the disease in a subgroup of patients. This therapeutic approach appears to be promising for patients that have a low pre-treatment thyroglobulin value (i.e., small tumour load).

Kidney toxicity is often the dose-limiting factor in therapeutic applications of radiolabeled peptides, particularly for energetic beta emitters. De Jong et al. (2004) have shown that the radiolabeled peptide ^{111}In-octreotide is distributed in a highly nonuniform fashion in human kidneys. The glomeruli, which form radiation-sensitive functional units for late radiation damage, are largely in the outer cortical regions of the kidney. However, they found most of

the radioactivity in the inner cortical zone. This accounts for the generally low radiotoxicity of radiolabeled peptides that emit particles with short ranges, such as Auger electron emitters, α-emitters, and low-energy β-emitters. A subsequent detailed radiation dosimetry analysis indicates the importance of considering these kidney radioactivity distributions when considering the biological effects of low energy electron emitters (Konijnenberg et al. 2007). Using a rat model, Rolleman et al. have recently demonstrated that colchecine can reduce kidney uptake of ^{111}In-DTPA-octreotide by 63%. D-lysine reduces uptake by 54%. When colchecine and D-lysine are given in combination, a 76% reduction was observed. This suggests that such pharmacologic approaches may also be used to reduce normal tissue toxicity associated with the therapeutic use of radiolabeled somatostatin analogs.

The capacity to achieve intranuclear targeting of tumor cells with ^{111}In labeled peptides has also been significantly advanced. Ginj et al. showed that a trifunctional N-terminal derivative of ((1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)0,-Tyr^3)octreotide (DOTA-TOC) bearing the nuclear localization signal (NLS) (of simian virus 40 large-T antigen) PKKKRKV was capable of delivering substantial amounts of radioactivity to tumor cell nuclei and with a high degree of retention (Ginj et al. 2005a, 2005b). Compared to the clinically used ^{111}In-DOTA-TOC, one N-terminal derivative exhibited a 45-fold higher accumulation in the cell nuclei and 6-fold increase in cellular retention. Another approach involves the use of ^{111}In and ^{123}I labeled immunoconjugates composed of 16-mer peptides derived from HIV-1 transactivator of transcription (tat) protein and anti-mouse IgG (mIgG) (Cornelissen et al. 2007, Hu et al. 2007). These constructs were prepared and used to label cultured BT-474 breast cancer (BC) cells. Data showed that the tat peptides promoted cellular penetration and nuclear uptake of radioactivity. As pointed out by (Boswell and Brechbiel 2005), these approaches offer significant advances in using Auger electron emitters for therapy.

Watanabe et al. (2006) have targeted human neuroblastoma cells which overexpress N-myc with ^{111}In-labeled phosphorothioate antisense oligonucleotides. Cell culture studies showed that when ^{111}In-labeled antisense hybridized with N-myc mRNA, N-myc expression was reduced and cell proliferation was inhibited. In vivo studies showed that when the treated neuroblastoma cells were inoculated intraperitoneally in nude mice, tumor growth was inhibited compared to controls. Based on these findings, they concluded that targeting of mRNA in tumor cells may be a valuable approach to treating cancer. Other ^{111}In labeled peptides for potential therapeutic applications have been created by He et al. (2004c). They have continued their progress toward the development of antisense/antigene radiotherapy approaches by chelation of peptide nucleic acid (PNA)-DTPA conjugates with ^{111}In. The PNA-DTPA-^{111}In was used to target single stranded DNA and breaks were measured. The PNA directed delivery yielded about ~0.1 SSB per decay, which was three times more than for ^{111}In labeled DNA-oligonucleotides. Based on these findings, they concluded that PNA oligomers may be very effective for antisense/antigene radiotherapy.

Reilly et al. (2004, 2006) have continued their development of ^{111}In-labeled human epidermal growth factor (hEGF) to target breast cancer cells that are hEGF positive. Pharmacokinetic studies in mice and rabbits indicate that ^{111}In-DTPA-hEGF can be administered at multiples of the maximum dose planned for phase I human trials without causing untoward toxicity to normal tissues.

Recently, the possibility of using the ubiquitous Auger electron emitter ^{99m}Tc for cancer therapy has been explored. Häfliger et al. (2005) have synthesized a trifunctional bioconjugate consisting of the SV40 nuclear localization signal (NLS) peptide, an aliphatic triamine ligand, and the DNA intercalating pyrene and labeled it with ^{99m}Tc. This radiopharmaceutical localizes in the cell nucleus of B16F1 mouse melanoma cells and

causes a much stronger radiotoxic effect than non-nuclear-localizing ^{99m}Tc complexes. Additional complexes have also been studied (Häfliger et al. 2005). According to the authors, these data suggest that with suitable targeting, ^{99m}Tc may be useful for therapeutic applications in addition to its widespread use for diagnostic imaging. Schipper et al. (2007) have recently studied the therapeutic potential of ^{99m}Tc-pertechnetate in nude mice carrying sodium/iodide symporter (NIS) expressing neuroendocrine tumor xenografts. They found that ^{99m}Tc provided substantial tumor control; however, considerable normal tissue toxicity was present that necessitated premature sacrifice of the animals.

Antiangiogenesis approaches to cancer therapy are well established. McQuade et al. (2004) have considered the possibility of using ^{125}I as an antiangiogenic agent. They used ^{125}I labeled biostatin, a member of the disintegrin family of polypeptides, to target αvβ3 integrins in EMT-6 mammary carcinoma tumors. A maximum tumor uptake of 11.7% ID/g occurred 2 h post-injection. These data suggest that radiolabeled ligands of this type may be suitable for antiangiogenesis tumor ablation.

Chen et al. (2006a) have designed a new approach to targeting tumor cells that involves delivering a water-soluble ^{125}I-labeled quinazolinone prodrug to the tumor cells whereupon it is enzymatically hydrolyzed to a water-insoluble form that precipitates. Intratumoral injection of this prodrug resulted in ~70% retention of the initially injected activity. Popisil et al. (2007) have identified prostatic acid phosphatase (PAP) as an enzyme overexpressed in prostate cancer and secreted in the extracellular space. Theoretical simulations showed that the prodrug ammonium 2-(2-phosphoryloxyphenyl)-6-iodo-4-(^{3}H)-quinazolinone (IQ_2-P) could be favorably docked into PAP. Autoradiographic studies with human prostate tumor cells showed that the radioiodinated prodrug accumulated around the cells. These and other data indicate potential for this enzyme mediated approach to cancer diagnosis and therapy (Wang et al. 2007).

The Auger emitter ^{125}I was tested for its capacity to eliminate measles virus infection (Dingli et al. 2005). Cells were infected with a recombinant measles virus expressing the sodium iodide symporter (MV-NICE) and then exposed to Na^{125}I. Effective control of MV-NICE was obtained in cultured cells. However, preliminary in vivo studies were not similarly effective. Nevertheless, the use of Auger electron emitters to fight viral infection is intriguing.

Among the many considerations for therapy is choosing the optimal radionuclide, a topic that has been discussed extensively. Recently, Uusijärvi et al. (2006) evaluated a variety of Auger electron emitting radionuclides for their capacity to irradiate tumor tissue while minimizing the absorbed dose to normal tissues. Their analysis, which takes into account the subcellular distribution of radioactivity in tumor tissues and absorbed dose to healthy tissues, suggests that the Auger emitters with the most promise for cancer therapy from a purely dosimetric standpoint are ^{58m}Co, ^{189m}Os, ^{103m}Rh, ^{193m}Pt, and ^{195m}Pt. The latter two radionuclides have received substantial attention in the past because they emit *in excess of 30* Auger electrons per decay on average and they have been shown to be highly radiotoxic (Howell et al. 1986, 1994, Azure et al. 1992). However, issues related to specific activity have precluded their further advance. Avenues of producing carrier-free ^{193m}Pt have been suggested, specifically ^{192}Os(α,3n)^{193m}Pt which has a cross section of 0.5 b with 40 MeV α-particles (Howell et al. 1986, 1994, Azure et al. 1992). This approach may be feasible in light of the recent work by Hilgers et al. (2005) who carried out ^{192}Os(p,n)^{192}Ir. Strategies have also been devised to increase the specific activity of ^{195m}Pt by about 100-fold, a major advance in the use of this potent Auger electron emitter (Knapp et al. 2005). Based on this development, one may anticipate that further progress will made in the therapeutic use of these platinum radionuclides.

The future of Auger processes in biology and medicine

Through the efforts of a relatively few number of scientists, many substantial advances have been made in terms of our understanding of the biological effects of Auger processes and their application in medicine. A puzzling dichotomy of opinions remains with respect to the significance of Auger electrons in terms of their biological effects. They are often largely ignored by international organizations that assess radiation risks, while, at the same time, their extreme radiotoxicity is touted as the perfect precision strike against disease. One can only conclude that there is much to learn about these curious electrons which have seemingly impotent energies when considered alone, but deposit an unparalleled density of energy when emitted as a shower of low-energy electrons.

An area of intense research on Auger processes has been DNA damage. As described above, recent advances in site-specific targeting *and* damage assessment will likely facilitate further discoveries regarding DNA damage and repair. No other source of radiation has this targeting capability. At present, these studies have been largely limited to plasmid DNA, however, their implementation in cultured cells and in vivo can readily be envisioned. Also brought to the fore is the potential for Auger processes to be used for elucidating molecular structure. This approach was introduced at the last Auger Symposium in Melbourne. While an extremely potent cascade of Auger electrons may be desired for treating cancer, more delicate radiation patterns may be useful for these and other applications of these radionuclides. For example, Panyutin et al. proposed the use of Auger emitters for gene therapy (Panyutin and Neumann 1994, Panyutin et al. 2000). In these instances, there may be scope for using ‘softer’ Auger electron emitters that impart the least amount of collateral damage. Radionuclides that decay by electron capture to the ground state of a stable daughter atom may be useful for such applications. Such radionuclides emit only Auger electrons and X-rays. There are few such radionuclides with suitable physical half-lives, perhaps ^{71}Ge may be ideal with a half-life of 11.4 d.

The most active area of research over the past four years has clearly been therapeutic applications of Auger electron emitters. Each meeting brings further evolution of existing strategies as well as new and novel therapeutic strategies. One important challenge to overcome in the therapeutic use of these radionuclides is differential uptake of radiopharmaceuticals by tumor cells even under ideal conditions where all the cells are exposed to the same drug concentration. Recent studies have suggested that log normal distributions of radioactivity among cell populations are likely to be the norm and that the breadth of this distribution can have a profound impact on a given radiopharmaceutical’s capacity to sterilize the tumor tissue (Neti and Howell 2006). This is particularly significant for Auger electron emitters whose toxic effects are largely a result of the high self-dose to the labeled cells. With this in mind, Auger electron emitting radiopharmaceuticals that target cell populations more uniformly may ultimately be the most effective therapeutic agents. Compounds such as ^{125}I-labeled Hoechst-33342 and -33258 enjoy highly uniform uptake which is why their unlabeled form is often used as a reagent for cell cycle analysis. While these examples may not have the targeting specificity that is desired, strategies that increase the uniformity of their uptake is something to strive for in the design of new Auger electron emitting radiopharmaceuticals and agents for photon activation therapy.

It is likely that Auger electron emitters can be used to make important discoveries in other fields of study as well. For example, Hofer (1992) suggested that the study of the aging process may benefit greatly from their use. Other topics include memory and cognitive function. This is an area of intense interest to the National Aeronautics and Space Administration (NASA) as they prepare for a manned space mission to Mars, a venture during which astronauts will receive sizeable absorbed doses from high-LET heavy ions.

Finally, one can envision the use of their precise targeting capability to gain insight into human fertility.

In conclusion, it was stated in a recent book by a well-known author that we have reached the end of the scientific age and no more major breakthrough discoveries will be made (Horgan 1996). This bleak outlook might daunt many scientists; however, similar prognostications have been made for centuries. The unique capacity of Auger electrons to deliver highly localized doses of radiation that are largely confined to nanometer dimensions make them potential tools for making breakthrough discoveries in the biological sciences. Only a small cadre of close-knit scientists with limited means have ventured into the arena of Auger processes. Much remains to be discovered by new scientists entering the field.

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