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BIOPHYSICAL ASPECTS OF AUGER PROCESSES

A review

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Radionuclide decay by electron capture and/or internal conversion is accompanied by complex atomic vacancy cascades and emission of low-energy electrons, resulting in a highly charged daughter atom and a high density of electron irradiation in the immediate vicinity of the decay site. The molecular and cellular consequences of such decay events include DNA strand breaks, mutations, chromosome aberrations, malignant transformation, division delay, and cell death. Damage to cells depends largely on the intracellular location of the radionuclide. Decays outside the cell nucleus produce low-LET-type radiation effects (RBE ~ 1). In contrast, decays in DNA cause pronounced high-LET-type effects (RBE ~ 7–9). However, recent studies suggest that even for DNA-associated Auger emitters cell damage can be modified to resemble the pattern observed with low-LET radiations. These findings indicate that the molecular and cellular mechanism(s) responsible for the cytotoxic effects of Auger emitters remain obscure.

In 1991, the Second International Symposium on Biophysical Aspects of Auger Processes started with an outstanding Opening Address by S. James Adelstein (1). In this lecture Adelstein presented a brief summary of earlier work and an in-depth review of more recent studies in the field. On opening this Third International Symposium I thought it profitable to follow his lead and to focus my review on a few principal themes, including physical aspects of Auger processes, molecular and cellular effects, and the implication of these studies for potential clinical applications in diagnostic and therapeutic nuclear medicine.

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Physical aspects

The 'Auger effect' was discovered in 1925 when the French physicist Pierre Auger noted multiple electron tracks emanating from atoms undergoing inner shell electron transitions after exposure to low-energy x-rays (2). It was later realized that Auger electrons are also emitted from certain radionuclides during radioactive transformation, but the biological significance of this effect was not appreciated because the energy carried by Auger electrons is usually negligible compared with the total energy released from the decaying radionuclide. However, during the early 1970's it became apparent that conventional dosimetry (which ignored highly localized energy deposition from low-energy electrons) was inadequate to explain the extreme biological toxicity of Auger emitters incorporated into the DNA of mammalian cells (3–6).

Early efforts to calculate electron spectra for Auger emitters provided data on electrons emitted from inner shells, but not from N- and O-shells (7, 8). This was later remedied by Charlton & Booz (9) who developed a Monte Carlo computer program to simulate individual radionuclide decays and to calculate Auger electron spectra for ^{125}I that included the very low-energy Auger electrons from

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outer atomic shells. Spectra of similar detail were subsequently published by a number of authors for ^{123}I, ^{64}Cu, ^{77}Br, ^{75}Se, ^{51}Cr, ^{111}In, ^{201}Tl, ^{55}Fe, ^{193m}Pt, ^{195m}Pt and several other Auger emitters (10–16).

This work was recently reviewed and critically evaluated in several reports prepared by a task group of the American Association of Physicists in Medicine. In one of these reports Howell (17) provided detailed electron spectra for several widely used Auger emitters, with the calculations based on a combination of assumptions and techniques previously used by himself and other authors. Howell's report (17) and a companion report by Humm et al. (18) showed that a surprising degree of uncertainty still exists in this field. For example, when the radiation dose from 1 Bq of ^{125}I is calculated for a 10-nm diameter sphere, the MIRD electron spectrum (19) suggests a cumulative dose of 2.32×10^8 Gy/Bq-h. By comparison, Howell's method (17) yields a dose of 8.55×10^8 Gy/Bq-h, and calculations performed according to Pomplun et al. (20) produce a dose value as high as 17.4×10^8 Gy/Bq-h. The differences become smaller as the diameter of the sphere is increased from 10 nm to 20 nm, but they are still large (0.56×10^8, 1.60×10^8, and 2.68×10^8 Gy/Bq-h respectively).

The key problem lies in the assumptions made for calculating electron spectra. For decays occurring in condensed phase it is usually assumed that the electrons emitted during the vacancy cascade are replaced by new electrons arriving as fast as needed to replenish the electron shells. As pointed out by Pomplun et al. (20), this assumption may not be valid and may produce results that in some cases significantly violate energy conservation. To correct this problem, Pomplun et al. (20) developed a computer program that achieves energy balance for simulated decay events by taking into account energy differentials at each stage of the decay process. However, even this sophisticated approach does not address some fundamental problems such as the range over which the residual ionization potential of the daughter atom should be applied.

It appears, therefore, that after a quarter century of intensive research we still cannot be completely certain about the number and energies of Auger electrons emitted during electron capture decay. The resulting uncertainties in dose calculations are not overly important for target volumes with a diameter above 1 μm, but for microvolumes with a diameter below 50 nm the discrepancies might be substantial (17). This becomes an important consideration in molecular studies where the goal is to determine whether molecular damage by Auger emitters is caused by high levels of radiation energy, charge effects, atomic transmutation, or by a combination of these factors.

Molecular effects

Damage from Auger electrons has been studied in a variety of chemical systems, but for obvious reasons investigators have focussed on DNA, the presumed target for radiation-induced cell death. Early work by Krisch et al. (21, 22) and Painter et al. (23) demonstrated that DNA-associated ^{125}I induces double-strand breaks (DSBs) in cellular DNA with nearly 100% efficiency. Martin & Haseltine (24) confirmed these findings and showed that ^{125}I decays are highly efficient in producing DNA single-strand breaks (SSBs) within 10 bases of the decay site in both the labeled and unlabeled DNA strand. Studies by Yasui (25) suggested that DNA damage by ^{125}I may involve clusters of lesions or multiple fragmentation events, and such severe lesions may in some cases provide little or no chance for effective repair.

However, interpretation of DNA damage as a function of energy deposition around the decay site remains problematical, particularly for Auger emitters that are not covalently linked to DNA. In part, the problem can be traced to differences in the assumptions used for calculating electron spectra for Auger emitters. Humm et al. (18) illustrated this problem for ^{125}I by calculating the mean energy deposition in DNA as a function of the location of the decay site relative to the DNA axis. With decays occurring at 0–0.5 nm distance from the DNA axis, energy deposition in the DNA was about 200 eV when calculated according to Pomplun et al. (20), 400 eV or 500 eV (without or with charge neutralization) according to Charlton & Booz (9), and 600 eV for the electron spectrum calculated by Howell (17). For decays located 2.5 nm or more from the DNA axis, all three electron spectra yielded nearly identical results, with energy deposition in the DNA falling to about 50 eV. The authors state that such differences in calculated energy distribution need not result in equivalent differences in DNA damage, but a 200–600 eV range in values for local energy deposition does suggest caution in interpreting microdosimetry data for Auger emitters.

Nevertheless, some promising new methods for theoretical modeling of DNA damage by Auger electrons have been introduced in recent years. Pomplun (26) developed a computer program for evaluating direct and indirect effects of ^{125}I decays in DNA. This program is based on a detailed model of DNA where the space occupied by each individual atom is represented by its van der Waal's radius, and all the free spaces inside the DNA are assumed to be filled with water. By overlaying Auger electron tracks generated by the MOCA8 code of Paretzke (27) the energy deposited in each atom is calculated. Energy deposited within the van der Waal's radius of atoms in DNA is counted as a direct radiation hit, and energy absorbed in the water phase represents indirect effects. Assuming a 10 eV energy threshold for SSB induction by direct hits and 17 eV by indirect interactions, direct and indirect effects account for 0.36 and 0.43 DNA DSBs/decay respectively. In addition, 0.15 DSBs/decay would occur as a result of combined direct and indirect effects on opposing strands within 20 basepairs of each other, providing a

total yield of 0.94 DSBs/decay. This model was later modified by raising the threshold for direct hits to 18 eV and considering only $OH^{\cdot}$ and $H^{\cdot}$ radicals out of all possible radiochemical species (28). This reduces the number of DSBs/decay to 0.6, again with the majority of the breaks induced by indirect interactions.

To provide a more realistic simulation of radiation damage under cellular conditions, Terrissol (29) and Pomplun & Terrissol (30) extended the DNA work to include modeling of ^{125}I-induced damage in nucleosomes. The nucleosome model was represented as a DNA double-helix with 146 basepairs and more than 9 000 atoms surrounding the histones. A complex combination of computer models permitted simulation of Auger electron spectra, time-dependent electron track structure calculations, scoring of direct electron hits at 10^{-15} s, and simulation of water radical behavior as a function of time up to 10^{-8} s. The results were similar to earlier data for a nucleosome model developed by Charlton & Humm (31), but the new calculations suggest that much higher energy values are needed to obtain biologically significant damage. According to Charlton and Humm an ^{125}I decay that deposits 400–450 eV in DNA induces two or more DNA DSBs with 60–70% probability, but according to Pomplun and Terrissol more than 1 200 eV need to be deposited to achieve this yield of DNA DSBs. Another interesting aspect of the nucleosome work is that it may provide some insight in the relationship between the microdistribution of DNA DSBs and cell death. For example, the model predicts that on the average about one in fifty ^{125}I decays results in two local DNA DSBs by direct hits. This correlates well with the finding that in many mammalian cell lines 30–60 ^{125}I decays/cell are required for cell inactivation.

Actual experimental results on molecular damage by Auger electrons include a report by Makrigiorgos et al. (32) who examined DNA damage induced by DNA-bound ^{123}I and ^{125}I in frozen V79 cells. Using the neutral elution assay for quantifying DSBs, the authors concluded that ^{125}I produces 1.34 times more DNA DSBs than ^{123}I. If it is assumed that each ^{125}I decay induces one DNA DSBs, ^{123}I would, on average, produce 0.74 DSBs/decay. The 1.34 ratio for ^{125}I vs ^{123}I compares to a theoretical ratio of 1.57 (or 0.64 DNA DSBs/^{123}I decay) predicted by Monte Carlo calculations performed according to the model of Charlton & Humm (31).

In another interesting report, Sahu et al. (33) evaluated the effect of ^{111}In decay on pBR322 plasmids by mixing supercoiled plasmid DNA with $^{111}InCl_3$, with or without a chelating agent that prevents indium binding to DNA. After accumulating ^{111}In decays under both conditions, the DNA was resolved by gel electrophoresis into supercoiled, nicked circular, and linear forms, representing undamaged DNA, SSBs, and DSBs respectively. The results showed that ^{111}In not bound to DNA produced approximately the same yield of DNA SSBs as observed with gamma photons from a ^{137}Cs radiation source. However, when the radionuclide was bound to DNA, the yield of SSBs was about 2.6 times greater even though only 15% of the ^{111}In was actually bound to DNA. In theory, induction of SSBs could have increased by a factor of 11 if all the ^{111}In activity had been bound to DNA. Surprisingly, DSBs induction was virtually identical under both experimental conditions, so it appears that the increased effectiveness of ^{111}In bound to DNA results primarily from a higher yield of SSBs.

A highly innovative paper by Panyutin & Neumann (34) examined DNA DSBs induced by triplex-forming oligonucleotides labeled with ^{125}I. In these studies an oligonucleotide complementary to the nef gene of the human immunodefficiency virus (HIV) was synthesized and labeled with ^{125}I at a deoxycytosine residue. The labeled oligonucleotide was then incubated with a plasmid containing a fragment of the nef gene. After confirming that DNA triplexes had formed, the sample was stored at −20°C for accumulation of ^{125}I decays. Subsequent analysis by electrophoresis revealed that ^{125}I decays in the oligonucleotide had caused DNA DSBs within the nef gene with an efficiency of ~0.8 breaks/decay. Mapping of the DSB sites with single base resolution showed that the breaks were distributed within 10 basepairs around the decay site. These findings demonstrate that ^{125}I decays induce DSBs even under conditions where the radionuclide is located on a separate DNA strand attached to the double helix in the form of a triplex. The results also suggest that Auger emitters may offer a unique approach for molecular targeting of specific gene sequences in a very large genome.

Cellular effects

The extreme cellular toxicity of Auger emitters has fascinated investigators for more than 20 years. Already the very first reports (3–6) demonstrated that ^{125}I incorporated into DNA was immensely toxic to mammalian cells. These initial studies were confirmed and extended by a number of investigators who showed that ^{125}I decays in DNA were very efficient in inducing DNA DSBs, mutations, chromosome aberrations, malignant transformation, division delay, and cell death (21, 22, 35–40).

It was soon recognized, however, that the biological effects of Auger emitters varied greatly with intracellular location (41). Auger emitters located in the cell nucleus were extremely cytotoxic, but identical decay events at extranuclear sites proved to be relatively nontoxic to cells (10, 42–44). Microdosimetry studies by Hofer (41), Yasui & Hofer (44), Charlton & Booz (9), Makrigiorgos et al. (46), and other authors (12–16) revealed that the striking change in cytotoxic action for Auger emitters located in different cell compartments was the result of

marked differences in energy distribution. This was confirmed in recent reports by Goddu et al. (47) and Faraggi et al. (48). The latter paper showed the subcellular dose distribution in cells exposed to ^{67}Ga, ^{99m}Tc, ^{111}In, ^{123}I, and ^{201}Tl. The radionuclides were assumed to be homogeneously distributed throughout the cell, or localized in specific cell compartments (nucleus, cytoplasm, plasma membrane). Using the cell nucleus and the plasma membrane as examples, the results indicate that the electron dose rate delivered to the nucleus is between 18 to 94 times higher if the five radionuclides are localized within the cell nucleus than if they are situated only on the cell membrane.

The results of biological studies generally conform to the pattern predicted by microdosimetry calculations. For example, in one experiment 60 ^{125}I decays at the DNA were sufficient to cause 50% cell death, but when ^{125}I was attached to the plasma membrane ~20 000 decays/cell were required to produce the same effect (43). Other early studies produced similar results and confirmed that Auger emitters decaying at extranuclear sites act as low-LET radiation sources with an RBE of ~1 (10, 42, 43). Jonkhoff et al. (49) compared the biological effectiveness of ^{67}Ga (located preferentially in the cytoplasm) to that of low dose rate exposures with gamma photons. The results indicated that ^{67}Ga decays yield an RBE of 1 for cell survival, 1.5 for G_2 arrest, and 1.8 for proliferation inhibition. Ludwikow et al. (50) noted a similar divergence in micronucleus formation in cells exposed to nuclear and cytoplasmic ^{125}I decays from ^{125}I-labeled thyroid hormone. Narra et al. (51) demonstrated an RBE of ~1 for ^{123}I and ^{125}I decays in the cytoplasm of mouse spermatogonial cells. In fact, in another report Narra et al. (52) showed that for cytoplasmic ^{51}Cr the RBE can be as low as 0.34, one-third of the RBE value obtained with external x-rays. This was attributed to the fact that ^{51}Cr has a small yield of high-energy gamma photons (0.11 photons/decay) and no dosimetrically significant electron component capable of penetrating more than 1 μm in biological material. Therefore, very little of the electron energy is deposited in the cell nucleus (except at the periphery), and the RBE falls below 1.

Although not overly effective at extranuclear locations, Auger emitters in the cell nucleus are highly radiotoxic and produce effects similar to those observed with alpha particles or other high-LET radiations (53). Kassis et al. (54) suggested that Auger emitters covalently bound to DNA are equally radiotoxic when differences in energy deposition are taken into account. They found that, in spite of substantial differences in the electron spectra, ^{77}Br (7 electrons/decay), ^{123}I (11 electrons/decay), and ^{125}I (20 electrons/decay) yield essentially the same RBE value of ~7 for cell killing in the V79 cell line. However, the magnitude of the biological effects is not always directly correlated with intranuclear energy deposition. Auger emitters localized in the cell nucleus, but not covalently bound to DNA, are somewhat less toxic and yield RBE values for cell killing of ~4–5 as compared to ~7–9 for covalently bound emitters (15, 55, 56).

In spite of differences in RBE values, most cellular data are consistent with the notion that intranuclear Auger emitters induce high-LET-type radiation damage. However, recent findings indicate that the toxic effects of Auger emitters can be mitigated by chemical radioprotectors. It is well known that chemical protectors are most effective with low-LET radiations; the protective action declines with increasing LET and becomes negligible for high LET radiations. Thus, it would be expected that chemical radioprotectors should not be very effective with DNA-associated ^{125}I. Nevertheless, Rao et al. (57), Narra et al. (58, 59), and Harapanhalli et al. (60) were able to demonstrate remarkable protection against ^{125}I damage in mouse spermatogonia by a variety of radioprotectors (MEA, AET, vitamin C, vitamin A). In contrast, little or no protection was noted in spermatogonia exposed to alpha particles from ^{210}Po under identical treatment conditions. These findings were interpreted as indicating that damage by DNA-associated Auger emitters is mediated by radicals and hence must be indirect in nature. This challenges the widely held view that Auger emitters behave like high-LET radiations that induce biological damage primarily by direct action.

Equally unexpected findings by Hofer et al. (61–63) also suggest that ^{125}I decays in DNA do not invariably kill cells by high-LET radiation action. When CHO cells were pulse-labeled with ^{125}IUdR and then harvested and frozen for accumulation of ^{125}I decays at different times after labeling, the biological effects showed a marked shift in the pattern of cell death. Cells harvested within 1 h after labeling yielded a typical low-LET radiation–survival curve with a pronounced shoulder and a large D_0 of 135 decays/cell, but identically labeled cells harvested 5 h after labeling showed a response characteristic of high-LET radiation without a shoulder and a D_0 of 42 decays/cells. A similar shift in ^{125}I action was observed for micronucleus induction (63), but not for the induction or rejoining of DNA DSBs (Hofer et al., this volume). These findings indicate that the high-LET-type damage induced by ^{125}I decays in DNA is not always reflected in a corresponding high-LET-type pattern of cell killing. To account for this discrepancy, the authors postulate the DNA DSBs may not be the sole cause of cell killing and that damage to higher-order chromatin structures in the cell genome may contribute to (or modify) radiation-induced cell death.

Therapeutic potential

In spite of the difficulties encountered in interpreting biological damage from low-energy electrons, the basic conclusion from cellular studies remains unchanged: Auger

emitters can be very toxic or relatively nontoxic, depending on whether they decay inside or outside the cell nucleus. This has important implications for medical applications. The most obvious one is that for diagnostic applications, where it is desired to keep cellular damage as low as possible, radiopharmaceuticals should remain localized outside the cell or at least outside the cell nucleus. Conversely, if Auger emitters were to be used for therapeutic applications, such as radionuclide therapy of cancers, it would be necessary to find radiopharmaceuticals that can selectively, or at least preferentially, introduce the radionuclides into the nuclei of cancer cells.

Radiation dosimetry plays a key role in evaluating the therapeutic potential of Auger emitters. Dosimetry calculations by Howell et al. (64) showed that low-energy electron emitters should be highly effective in treating micrometastases, but large tumors would respond better to high-energy β emitters. This work was extended by Strand et al. (65), and Humm et al. (18) who stressed that evaluation of radiopharmaceuticals for cancer therapy requires data on both the subcellular radionuclide distribution and the degree of heterogeneity in cellular activity within tumors. To develop a method for assessing radionuclide distribution in intact tissues, Humm et al. (66) performed a series of studies where monoclonal antibodies labeled with $^{114}In^{m}$ were injected into tumor-bearing mice, and the microdistribution of radioactivity in the tumor, spleen, liver, and kidneys was evaluated 24 h later by preparing 3D reconstructed serial autoradiographs of the tissues. The results showed that evaluation of the spatial distribution of radioactivity in tissues is complicated by tissue distortion, uncertainties in activity measurements of individual tissue sections, and imprecision in the 3D reconstruction of serial autoradiographs. The resulting errors in cellular dosimetry are relatively minor for high-energy β emitters, but become more serious for radionuclides that emit low-energy electrons.

An equally difficult problem is the development of suitable carrier compounds for targeting Auger emitters to cancers. The most frequently mentioned targeting agent is radiolabeled iododeoxyuridine (IUdR). Schneiderman & Schneiderman (67) have demonstrated the potential utility of IUdR in an elegant tissue culture system where they used ^{125}IUdR to 'cure' cancer in a mixed population of normal (WI38) and cancerous (HeLa) cells. In this experiment the two cell lines were co-cultured in a single growth flask, and ^{125}IUdR treatment was started after the normal WI38 cells had reached confluence and stopped cell division. HeLa cells continued cell proliferation and could thus be selectively labeled and eradicated without detectable adverse effects to the WI38 cells.

However, there are serious obstacles that complicate the systemic use of IUdR in intact organisms. First, the half-life of IUdR in the circulation of humans (68) and animals (69) is very short (5–7 min), making it difficult to achieve therapeutic radionuclide levels within cancers. In addition, most solid tumors contain extensive regions of nonproliferating cells that cannot be labeled by single injections of IUdR. As a consequence, repeated injections or continuous infusions are required to eliminate proliferating tumor cells and to recruit the non-dividing cells into active proliferation. Another complication arises from the fact that IUdR is utilized by proliferating cells in both normal and neoplastic tissues, i.e., prolonged treatment with high doses could cause severe toxic side-effects to host organs, such as the intestine or the bone marrow.

To overcome these problems attempts have been made to selectively target IUdR to tumors by direct infusion into the target area, or by injection into an arterial blood supply that precedes the tumor. Examples of this approach include studies by Van den Abbeele et al. (70) who found that intravesical administration of ^{125}IUdR into rats with bladder tumors leads to high tumor to normal tissue ratios of ^{125}I incorporation. Kassis et al. (71) demonstrated tumor-specific uptake of IUdR following intrathecal infusion into rats bearing brain tumors. Mariani et al. (72, 73) extended this approach to humans and demonstrated efficient radionuclide uptake in patients with colerectal cancer and breast cancer after intratumoral injection of ^{125}IUdR. A potential improvement over current methods of regional radionuclide infusion was proposed by M. H. Schneiderman and R. Lieberman (personal communication) who suggested that ^{125}IUdR incorporation into liver cancers could be increased by injecting IUdR into the hepatic artery and simultaneously blocking blood outflow from the liver with a balloon catheter. Before restoring free blood circulation, thymidine could be administerd to minimize subsequent incorporation of ^{125}IUdR into normal body tissues.

However, the utility of regional radionuclide treatments is limited by the fact that such strategies are effective only in the chosen treatment volume; they cannot be used to treat tumor metastases. This obstacle could be overcome by developing true tumor-seeking agents that selectively deliver radionuclides to cancer cells regardless of where they are located. In principle, tumor-specific antibodies could serve as selective carrier agents, but so far most trials with radioactively labeled antibodies have produced disappointing results. Problems include the failure to find cell surface groups (epitopes) that are truly unique to cancer cells, heterogeneity in the expression of epitopes, limited penetration of antibodies into solid tumors, and low levels of antibody attachment to tumor cells (74). If future research does yield clinically useful antibodies, it may be possible to employ such antibodies as cell-specific delivery agents for IUdR, DNA intercalating agents (e.g., propidium iodide) or other DNA-seeking molecules.

Another potentially useful approach to radionuclide therapy of cancers involves the use of radioiodinated hormones or anti-hormone drugs, for example estrogens or

tamoxifen. Work by Bloomer et al. (75), McLaughlin et al. (76), and DeSombre et al. (77) suggest that such agents can kill estrogen receptor positive cells with little or no cell lethality in estrogen receptor negative cells. The problem is that even ER+ tumor cells have only about 10 000–30 000 receptor sites per cell, and under in vivo conditions it is nearly impossible to saturate all (or even most) of the receptors with iodoestrogen molecules. However, as pointed out by DeSombre et al. (77), this limitation can be overcome by using ^{123}I-labeled estrogens with ultra-high specific activity (240 000 Ci/mmol) which facilitates substantial cell killing in ER+ cells even under conditions where the residence time of iodoestrogen in cells is relatively short.

Other potentially promising targeting agents include epidermal growth factor for certain cancers that over-express growth factor receptors (78), or anti-tumor drugs such as bleomycin or carboplatin labeled with Auger emitting radionuclides (79). Another interesting suggestion is to develop oligonucleotides capable of sequence-specific DNA triplex formation that could, at least in theory, offer the potential for radionuclide targeting to oncogenes in the cancer cell genome (80).

In addition, strategies employing artificial Auger cascades need to be further explored. In this case tumor cells are exposed to agents that become cytotoxic only when Auger cascades are induced by external irradiation. A striking example of this approach is the work by B. H. Laster and G. Shani (personal communication) who exposed V-79 cells to boronated porphyrin containing gadolinium, and then subjected the cells to a mixed radiation field. The results suggested an overall lethality enhancement factor of 5 at the 10% survival level, with almost half of this effect caused by Auger electrons emitted as a result of thermal neutron capture by gadolinium atoms.

Conclusion

The unique decay and dose distribution characteristics of Auger emitters provide avenues for investigating basic molecular and cellular mechanisms of radiation action that can often not be duplicated by external radiation sources. At the same time, Auger emitters hold great promise in radionuclide therapy of cancers if (and that is still a very big IF) suitable methods for preferential radionuclide delivery to cancer cells can be developed. As pointed out by Feinendegen (81), 'molecular surgery' by Auger emitters may one day provide a means of realizing Paul Ehrlich's dream of a 'magic bullet' in cancer therapy.

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