## Problems Associated with Oligonucleotide Radiotherapy

**TO THE EDITOR:** We read with interest the article by Sedelnikova et al. (*1*). Their study was about a hot topic and was experimentally well designed. The authors found that $^{125}$I-oligodeoxyribonucleotides (ODNs) were more radiotoxic than $^{125}$I-antipyrine or $^{125}$I-bovine serum albumin; the former freely dissociates into cells, whereas the latter remains outside the cells. However, they found that the radiotoxicity of unbound $^{125}$I-ODN was significantly lower than that of DNA-incorporated $^{125}$I-deoxyuridine (UdR). Therefore, we would like to address a few issues for further discussion.

Lower toxicity often indicates lower usefulness in therapeutic applications, not the opposite. Thus, the results of Sedelnikova et al. may mean that ODN radiotherapy should be dropped from further development in similar experimental settings because enhanced cytotoxicity was not observed. We do not believe that this is the case. Importantly, nuclear localization alone when using Auger emitters does not ensure high radiotoxicity but rather high dose to nuclear DNA, as they showed (*1*).

It is possible to modify and increase the efficacy of radiotherapy delivered by ODNs by selecting optimal labels and carriers for each localization of particular targets (*2,3*). In this case, $^{125}$I-ODN was much weaker than $^{125}$I-UdR because of a lower concentration in the cell nucleus.

Furthermore, the liposomal delivery system may alter observed radiotoxicity considerably, and, in fact, it was not used with reference agents in the study of Sedelnikova et al.

Earlier (*3*), we used the term "oligoradionuclidetherapy" to describe more precisely the nature of therapy. The authors' term, "gene radiotherapy," could be used to describe all radiotherapeutic methods involving genes or any method using that sort of vehicle.

### REFERENCES

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2. Kairemo KJA, Tenhunen M, Jekunen AP. Dosimetry of radionuclide therapy using radiophosphonated antisense oligodeoxynucleotide phosphorothioates based on animal pharmacokinetic and tissue distribution data. *Antisense Nucl Acid Drug Dev.* 1996;6:215–220.
3. Kairemo KJA, Tenhunen M, Jekunen AP. Oligoradionuclidetherapy using radiolabelled antisense oligodeoxynucleotide phosphorothioates. *Anti-Cancer Drug Des.* 1996;11:439–449.

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**REPLY:** We thank Dr. Kairemo et al. for their interest in our research. The points they mention in their letter are the result of confusion of two newly developing radiotherapy approaches: gene radiotherapy proposed by us (*1*) and oligoradionuclidetherapy (ODN-RT) developed in their interesting publications (*2,3*). Both approaches use oligodeoxyribonucleotides (ODNs) for delivery of radioisotopes to the targets. The principal difference between gene radiotherapy and conventional radiotherapy (including ODN-RT) is that the former is aimed against specific genes or genomic rearrangements in the genome of the target cells, whereas the latter is based on delivery of a higher dose of radiation to the tumor, to the tumor cells and, consequently, to the total DNA of the tumor cells, since DNA is the main target of ionizing radiation.

Our concept of gene radiotherapy is based on sequence-specific delivery of radionuclides to the selected target(s) in the genome. Vehicles for this delivery could be triplex-forming ODNs, which are currently under investigation in our laboratory, or any other DNA-sequence-specific agents (peptides, proteins, polyamines and others). The principal goal of gene radiotherapy is to damage only the targeted gene or specific site in the genome while producing minimal damage to the rest of the genome. Therefore, only radioisotopes with a range of damage comparable with the diameter of the DNA molecule (approximately 2.0 nm) are useful for gene radiotherapy. The only class of radioisotopes that satisfy such a condition are Auger electron emitters.

The fact that our observed radiotoxicity for $^{125}$I-ODN is significantly lower than that of DNA-incorporated $^{125}$I-deoxyuridine (UdR) (*1*) means that the nuclear DNA was "out of reach" for very short-range Auger electrons generated by decay of $^{125}$I in the case of $^{125}$I-ODN. We predict no difference in radiotoxicity of $^{32}$P-ODN and DNA-incorporated $^{32}$P-deoxythymidine, for example. Therefore, addressing the first point, we do not believe that Kairemo et al. should give up ODN-RT. With the right choice of radioisotope, it is a quite promising approach, as they showed (*2,3*).

In regard to the point raised about the liposomal delivery system, we do not have data on radiotoxicity of the reference agents ($^{125}$I-bovine serum albumin and $^{125}$I-antipyrine) delivered with liposomes. We agree that there is a possibility of redistribution of the above agents in cell culture in the presence of liposomes, although we do not believe that liposomes by themselves could affect dose dependence of cell survival curves.

### REFERENCES

1. Sedelnikova OA, Panyutin IG, Thierry AR, Neumann RD. Radiotoxicity of iodine-125-labeled oligodeoxyribonucleotides in mammalian cells. *J Nucl Med.* 1998;39:1412–1418.
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