Literature Review for Research Irradiators[1]

Research irradiators like other irradiators use Category 1 and 2 strength cobalt-60/cesium-137 sources for a variety of tasks.[2] Some applications are to test the ability of devices to withstand radiation, such as electronics placed in locations where the dose of radiation may be high such as in space or near nuclear reactors or particle accelerators. Others are for biomedical applications such as irradiating small or large animals or cells to test the effects of radiation dose or to facilitate other studies by deliberately weakening an animal's immune system (immunosuppression). These applications for research irradiators are the focus of this review.

Biomedical Applications of Irradiation

The irradiation of small animals such as mice, rats and fish is critical to studies where animals serve as stand-ins for human models (translational medical research). One of the effects of radiation is to suppress the immune system. Scientists can take advantage of this effect to purposely shut down the immune system of an irradiated animal. Scientists then transplant the bone marrow (a source of stem cells) of another non-irradiated animal into the animal with the suppressed immune system. [3] By essentially replacing the immune system of one animal with another they gain information into how genes develop and manifest and cells interact—that is how "immune cells regulate transplant rejection, infection, autoimmunity, tumor growth, and more". [4] The process is not immediate and takes weeks to work. The animal with a mix of its own cells and bone marrow from another animal is known as a chimera. For dogs, pigs, and primates, scientists transplant blood cells rather than bone marrow stem cells since they have much more blood than rodents. [5] Other animals such as Zebrafish are irradiated to permit transplants of tumor cells in order to see how previously healthy tissue responds when tumor cells are introduced and for identifying novel cancer therapies. If the dose of radiation is not high enough and the transplant is rejected the animal gets GVHD (graft-vs-host-disease) or develops other complications.

More recently interest has grown in using mice to mimic human radiotherapy treatment. Sophisticated equipment customized to small animals like millimeter sized cone-shaped beams under precision guidance are now used in pre-clinical investigations, and models of mice tumors are increasingly more advanced and clinically relevant. Non-isotopic technology is used rather than radioactive sources because scientists require very specific beam energy and other parameters in their experiments. The new machines can replace previously employed

---

[1] This paper draws heavily from Miles Pomper, Egle Murauskaite, and Tom Coppen, "Alternatives to High-Risk Radiological Sources: The Case of Cesium Chloride in Blood Irradiation," *Occasional Paper #19*, James Martin Center for Nonproliferation Studies, 2014

[2] The IAEA's code of conduct on the safety and security of radiological sources classifies radiation sources by their effect on the human body if unshielded and depends of the quantity and type of material. Category 1 sources are "likely to cause permanent injury to a person who handled them or was otherwise in contact with them for more than a few minutes."; For Category 2 sources the same effect would occur in "minutes to hours". [2]

[3] http://www.irpa.net/members/P06.84fp.pdf

[4] https://www.taconic.com/taconic-insights/oncology-immuno-oncology/rodent-irradiation-considerations.html

[5] Duran-Struuck, Raimon, and Robert C. Dysko. "Principles of bone marrow transplantation (BMT): providing optimal veterinary and husbandry care to irradiated mice in BMT studies." Journal of the American Association for Laboratory Animal Science 48, no. 1 (2009): 11-22.

technology, such as simple kilovoltage X-ray irradiators and radioisotope irradiators which had little ability to adjust the beam to target the dose on small tumors, so the animal's normal tissue also received a dose which is undesirable. [6]

Self-Shielded Radionuclide Irradiators

Self-shielded radionuclide irradiators are devices containing isotopic sources such as cesium-137 or cobalt-60 to create a radiation field. The sources, usually in a salt form, are encapsulated inside of a sealed steel cylinder to prevent the possibility of leakage. Such sources provide a dose to an animal of 1-5 Gy/minute. A dose of 10 Gy is generally fatal for mice. Access to the irradiation chamber is through a lead-shielded door and a collimator system can limit dose to particular areas. The source itself sits inside a guide tube and is moved to the irradiation position when irradiation commences and is not in the line of sight of the operator. Both the irradiation cavity and the source vault are shielded to prevent the operator from being exposed to the radiation. The sample-holder can be configured so that only one animal is exposed or it can be placed on a rotating turn-table to expose multiple animals. [7]

X-ray Irradiators and LINACs

X-ray tubes work differently from isotopic sources such as cobalt-60 and cesium-137. X-ray tubes use bremsstrahlung (breaking) radiation produced when electrons are rapidly decelerated and hit high atomic number metal targets. Through the process, photons are produced that range from zero to the maximum beam energy. Therefore, a 100 kilovolt beam can produce a maximum of 100 keV X-rays. X-rays are classified according to their energy: X-rays from 10 keV to 100 keV are known as superficial X-rays, while ones with energy from 100 keV to 500 keV are known as orthovoltage X-rays. The dose is delivered on a timer but the time for the shutter to open and close needs to be included in the analysis of the dose. With isotopic sources as soon as the shutter is opened the gamma rays produce a dose which makes it more complex to estimate the dose. In contrast, there is a few second delay until the X-ray tube produces a dose at the desired level. [8]

Linear accelerators (LINACs) can also produce high energy electrons and photon beams for animal irradiation. Rather than electronically producing X-rays, they accelerate electrons to high energies using microwaves; and produce X-rays when these high-energy electrons hit metal targets. However, they usually produce too much energy for small animal irradiation resulting in the animal receiving an excessive dose. [9]

Progress in Non-Isotopic Small Animal Irradiation

---

[6] Butterworth, K. T., K. M. Prise, and F. Verhaegen. "Small animal image-guided radiotherapy: status, considerations and potential for translational impact." The British journal of radiology 88, no. 1045 (2014): 20140634.

[7] Yoshizumi, Terry, Samuel L. Brady, Mike E. Robbins, and J. Daniel Bourland. "Specific issues in small animal dosimetry and irradiator calibration." International journal of radiation biology 87, no. 10 (2011): 1001-1010.

[8] Podgorsak, pg 215

[9] Yoshizumi, Terry, Samuel L. Brady, Mike E. Robbins, and J. Daniel Bourland. "Specific issues in small animal dosimetry and irradiator calibration." International journal of radiation biology 87, no. 10 (2011): 1001-1010.

X-ray tubes are a direct alternative to cesium-137 self-shielding sources. Companies market X-ray tubes specifically to replace isotopic sources. X-ray irradiators come with fewer security and disposal requirements than isotopic sources. Also, one publication estimated the cost of an X-ray irradiator is approximately one sixth of the cost of cesium-137 irradiator not accounting for other costs such as shipping and disposing of the cesium-137 source. [10] Another researcher asserted that when maintenance, regulatory costs, and decommissioning costs are taken into account the annual costs are commensurate. However, the cost burden may be shared differently within the institution, one modality may be less expensive than the other from the point of view of the cost to the researcher. [11]

The Nuclear Threat Initiative (NTI) investigated the operating, training, and regulatory and termination costs of switching from using cesium-137 radioactive source irradiators to X-ray irradiators. [12] In general, cesium-137 because of its potential to cause mass harm is more tightly regulated and has extensive security requirements. This contributes to substantial starting and recurring annual costs. Moreover, the NTI report stresses that there are also extensive hidden liability and termination costs to using cesium-137 irradiators that are typically not factored into customer's purchasing decisions For example, the report warns that should a source be stolen or go missing and be used to harm people or property, the facility may be held liable for billions of dollars in damage. In addition, the lifetime costs of end of life disposition of the sources is not reflected in the costs of purchasing the cesium-137 sources. The NTI report includes a useful worksheet for facilities to be able to assess whether switching to X-ray irradiators is cost effective. It notes that the US Government has a program to provide incentives for the replacement of cesium-137 sources with X-ray sources through the National Nuclear Security Administration's Office of Radiological Security Cesium Irradiator Replacement Project known as CIRP. The CIRP program takes ownership of the source and incurs the cost of disposition as well as pays for half the cost of a replacement non-isotopic irradiator such as an X-ray irradiator. The disposition cost alone could save the facility as much as two hundred thousand dollars. [13] [14]

Several studies have been conducted comparing technical aspects of cesium-137 and x-rays sources for research irradiators. For example, Mount Sinai hospital has initiated a series of studies and published a summary of the performance of the two modalities according to various relevant dosimetry parameters.[15] They reported that the dose distribution was more homogenous for the X-ray irradiator than for the cesium-137 source and noted there were significant differences in

[10] Gibson, Brian W., Nathan C. Boles, George P. Souroullas, Alan J. Herron, Joe K. Fraley, Rebecca S. Schwiebert, John J. Sharp, and Margaret A. Goodell. "Comparison of Cesium-137 and X-ray irradiators by using bone marrow transplant reconstitution in C57BL/6J mice." *Comparative medicine* 65, no. 3 (2015): 165-172.

[11] See video presentation by Keith Jenne, University of California San Diego, at the Cesium Irradiators Conferences [January 29-30, 2018, the University of California] from 1:04:00 at https://www.youtube.com/watch?time_continue=3903&v=ZKpUMx762zo

[12] Ioanna Iliopulos, Major Lifecycle Cost Considerations for Cesium-137 Irradiators and X-ray Irradiators, Nuclear Threat Initiative Report, Nov 2018. https://www.nti.org/media/documents/Major_Lifecycle_Cost_Considerations_II_Nov2018.pdf

[13] For details on CIRP program see brochure at: https://www.nti.org/media/documents/ors_cirp_brochure_r18_web.pdf

[14] For a details on liability/insurance issues see: Government Accountability Office (GAO) reports discussed at: https://www.nti.org/analysis/articles/lifecycle-cost-and-liability-considerations-cesium-137-irradiators/

[15] https://www.nti.org/media/documents/Mount_Sinai_Experience_paper_6-5-2017.pdf

the source geometry between the two cases. For example, in a cesium-137 irradiator with a rotating source holder mice are free to move to the edge or towards the center and this gives them a non-homogenous dose distribution. In contrast to an X-ray irradiator, where mice are confined towards the center of the irradiation chamber. The authors used a water and rodent phantom to determine the percent depth dose (dose at various depths normalized to the peak dose) for a 160 kVp X-ray beam and cesium-137. They reported that the percent depth dose measurements showed "very similar curves" for both phantoms but noted that the X-ray irradiator exhibited more backscatter. Mount Sinai also did some comparison studies for specific applications such as bone marrow ablation (cell death) which they found to be similar to cesium-137. They also studied the survival rate of 12 mice when only their brains were irradiated with a 10 Gy dose. They found that the mice survived which is also expected from cesium-137 irradiation.

A study by Gibson *et al* investigated cellular ablation of bone marrow compared to cesium-137. [16] After irradiating mice with doses of 0.5, 0.7, 0.9 and 1.1 Gy with both irradiator types the lethal dose was determined for a particular strain (known as C57BL/6J) of mice. The study concluded that "both sources were efficient at ablating endogenous bone marrow sufficiently to enable stem cell engraftment" but that for studies where the two sources are compared, "there are distinct physiologic responses that should be considered prior to choosing the optimal source for use in a study". The study also found that the morbidity was lower for cesium-137 compared to X-ray source which the study attributed to opportunistic infection.

A Monte Carlo analysis by Belley *et al* sought to find means of providing an equivalent biological effect when x-ray irradiators are substituted for cesium-137 machines. [17] They used a 320 kV Precision X-Ray irradiator with various thicknesses of filtration. Filtering the X-ray beam with certain metals shifts the spectrum to higher (harder) energies because the low energy photons are absorbed. However, the higher the thickness the more photons are absorbed so that the dose will be decreased. [18] The study found that an X-ray beam filtered with 4 mm HVL equivalent of copper best mimics the cesium-137 beam in terms of dose to bone and bone marrow and cell survival. [19] The purpose of the filter is to block low energy portions of the X-ray spectrum. The implication of this is that the dose will not vary much throughout the mouse for higher energy voltage machines compared to 160 kVp. In addition, the higher voltage machines will have a less effect on damaging the surface tissue.

---

[16] Gibson, Brian W., Nathan C. Boles, George P. Souroullas, Alan J. Herron, Joe K. Fraley, Rebecca S. Schwiebert, John J. Sharp, and Margaret A. Goodell. "Comparison of Cesium-137 and X-ray irradiators by using bone marrow transplant reconstitution in C57BL/6J mice." *Comparative medicine* 65, no. 3 (2015): 165-172.

[17] Belley, M.D., Ashcraft, K.A., Lee, C.T., Cornwall-Brady, M.R., Chen, J.J., Gunasingha, R., Burkhart, M., Dewhirst, M., Yoshizumi, T.T. and Down, J.D., 2015. Microdosimetric and biological effects of photon irradiation at different energies in bone marrow. Radiation research, 184(4), pp.378-391.

[18] https://www.nde-ed.org/EducationResources/CommunityCollege/Radiography/Physics/filters.htm

[19] HVL stands for Half Value Layer and is the thickness of any given material where 50% of the incident energy has been attenuated. https://www.nde-ed.org/EducationResources/CommunityCollege/Radiography/Physics/HalfValueLayer.htm

There are also mouse strain-dependent effects which need to be considered in comparison studies as some mouse strains are more sensitive to radiation than others. For example, the C57BL/6 strain is able to withstand doses far higher than the BALB/c mouse strain.

In order to help researchers, determine whether to use cesium-137 or X-ray irradiators, the University of California (UC) has pulled together a compendium of comparison studies that can be consulted. [20] Still, the small number of detailed comparison studies is evident. As a result, a working group of UC researchers has recommended that researchers conduct a comparison study between the two technologies particularly when the purpose of the irradiation is to kill cells in "a weakly dose-dependent manner for the purpose of ablation". This is an application where x-rays are seen as strong candidates for replacing cesium-137 sources with X-rays. However, even in the cases where the purpose of the technology is for other purposes, such as to convey a strong dose over a long period of time, the working group pointed to the possibility of using other non-isotopic sources such as unfiltered X-rays or perhaps research reactors. [21] The complexity of X-ray tube energy spectrum calibration must be done for every experiment, but the magnitude of the dose will be less important for some applications (such as determining the dose to destroy tumors) than others such as when blood is irradiated to prevent Graft-Versus-Host Disease. [22]

The Road Ahead

As discussed in the U.S. government's 2016 GARS (Interagency Working Group on Alternatives to High Activity Radioactive Sources) report when users replace cesium-137 with new technologies, new baseline experiments will need to be conducted "in order to demonstrate reproducible results equivalent to the cesium technology or determine a weighting factor to describe differences in the outcomes". [23] A concerted effort needs to be carried out to characterize the differences between cesium-137 and orthovoltage X-rays for specific biomedical irradiation applications where cesium-137 is used currently. The goal of such an effort should be to come up with a standard protocol for characterizing an X-ray beam in relation to existing cesium-137 devices for specific applications.

There are many advantages for X-ray sources compared to cesium-137, not only because of security restrictions, and ease of disposal, but also because cesium-137 sources today are difficult to procure. Studies should be performed such as determining the Relative Biological Effectiveness (RBE) for various biological materials *in vivo*, *in vitro* and through Monte Carlo simulation so that the dose distribution of X-ray sources with specific filters can be better understood. Yoshizumi *et al* and others have suggested other experiments to help appropriately calibrate X-ray beams that

[20] https://drive.google.com/drive/folders/1l-nVq2dN68IPxoad00qVbO-AoXfb1wUs

[21] B. Smith et al, University of California Systemwide Radioactive Source Replacement Workgroup Recommendations, April 30 2018. e

[22] ibid

[23] https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/ndrd-gars_best_practices_guide_final-.pdf

would study the dose rate as a function of beam energy, tube filtration, variation with source to target distance, etc.

While irradiation of small animals and cells with X-rays is essentially equivalent to cesium-137, the problem lies with other applications such as large animals, and radio-resistant bacteria for which X-ray irradiators cannot provide the required dose and LINACs are needed. [24] However, so much progress is being made in technology and analysis for precision small animal radiotherapy that it may be possible that the need for large animal irradiation will decline over time. Sophisticated image-guidance systems which can truly "mimic clinically advanced treatments in experimental settings" done with mice rather than large animals will further make cesium-137 less relevant. [25]

Finally, there is a general movement in science arguing that when results are reported in publications that a "recipe" should be given versus just a "list of ingredients", that is, providing enough information in experimental results that the experiment can be truly reproduced. [26] This is what Statistician Philip Stark (University of Berkeley) calls 'prereproducibility'. One could imagine that in publications that use X-ray irradiators or Cesium-137 irradiators that enough detail is provided that careful comparisons can be made between the two modalities. Details such as the depth of the beam for maximum dose relative to the animal for whole body irradiation should be explicitly described in an online appendix to a publication. For example, details such as differences in the specifications of X-ray tubes, energy settings and filtration need to be clearly documented. It was found that these varied even across the same model X-ray tubes. [27]

One way of pulling this information together would be for a reputable journal or organization or governmental bodies like the IAEA or US. National Nuclear Security Administration to document such activities in a dedicated database comparing procedures and results for specific contexts. Once enough studies have been conducted, an in-depth, independent, systematic, comparative analysis can be done to determine what the differences in various relevant parameters are for practical research.

[24] Rhesus macaque were irradiated using a 6 MeV LINAC to determine dose-response. See: https://www.nist.gov/sites/default/files/documents/2017/05/09/FT19MacVittie.pdf

[25] Verhaegen, Frank, Ludwig Dubois, Stefano Gianolini, Mark A. Hill, Christian P. Karger, Kirsten Lauber, Kevin M. Prise et al. "ESTRO ACROP: Technology for precision small animal radiotherapy research: Optimal use and challenges." Radiotherapy and Oncology 126, no. 3 (2018): 471-478.

[26] Stark, P. B. "Before reproducibility must come preproducibility." Nature 557, no. 7707 (2018): 613.

[27] B. Smith et al, University of California Systemwide Radioactive Source Replacement Workgroup Recommendations, April 30 2018. https://www.nti.org/media/documents/Radioactive_Source_Replacement_Working_Group_Recommendations_05_02_18_FINAL.pdf