Molecular Therapy

1. Molecular Therapy Using Auger Electrons

Molecular Therapy (MT) is the cellular modifications at the molecular level. Take the chemotherapy in oncology for example, it aims to kill the cell by delivering toxic agents to the cell, while MT could aim to terminate the cellular division without necessarily killing the cell, such as aiming to reach senescence whose therapeutic procedure, levels of toxic agents, and tools for delivering the toxicity could all be very different from simply killing the cell.

An example of the senescence therapy could be the delivering of ^{77}BrdC to a Herpes specific gene responsible for certain cancer transformation. Helson and Wang applied the radioactive bromide compound that has a K-capture decay mode leading to a mega Gray (Gy) dose with Auger electrons *in Situ* [1] at the DNA level that terminates the cellular division and drives the cell into a state of senescence. But the mega Gy dose is limited to a dimension of a few nanometers so that while it modifies both of the DNA duplexes, it does not interrupt other cellular apparatus sufficiently to kill the cell. This *in Vitro* work was carried out at Sloan-Kettering Cancer Center in the 1970s, and the work was not published as it was meant to be the beginning program of an extensive clinical trial. The Auger dose in mega Gy can be found in Wikipedia under "Auger Therapy" [1].

Using ^{77}BrdC to exclusively inhibit the Herpes specific DNA material, its *in Situ* mega Gy delivered by the localized low energy Auger electrons with an ionizing range of a few nanometers in water could modify both of the DNA duplexes and terminate cellular division. Phosphide sugar or the BrdC, however, could be separated and deleted by liver enzymes *in Vivo* to result with the loss of the specific uptake by the Herpes gene exclusively. While "nuclear chemotherapy" using radioactive material for chemo agent, as Lewis Thomas named such an approach, it suffers from the liver interference *in Vivo*. As a result, a similar *in Situ* dose has been designed by using an external X-ray beam, the monochromatic "Nano Ray X-rays" to bypass the liver interference in drug delivery [2], and thus the development of the "NanoRay" X-ray tool that could be used to induce the mega Gy Auger dose without using radioactive elements. The external monochromatic X-ray photons are beamed to resonantly react with strategically placed target atoms such as the platinum of cisplatin attaching to the major groves of the DNA adducts, and they could be induced to initiate the mega Gy dose *in Situ* to modify both of the DNA duplexes and terminate cellular division without necessarily killing the cells. This senescence approach implies a dramatic reduction in systemic chemo toxicity as well as dose reduction in the externally placed ionizing beam radiation. This approach allows the procedure to be applied repeatedly to deliver the localized termination of cellular divisions and the procedure with minimal side effects could be addressed as often as necessary.

We shall use cisplatin, the chemo agent [3] as a case in point to illustrate the power of this method. Cis (on the same side)-platin has two amino ligands on one side and two chloride ligands on the other side with Pt being centered in the plano molecule, whose Cl-bonds would leave Pt ion upon entering the cytoplasm as the leaving group because of the reduced NaCl concentration and thus the reduced Chloride ionic pressure to form the "leaving group". The bonds for chloride would be replaced by the aqua bonds which would bind to two purine bases, with Guanine favored over Adenine in the major groves of DNA adducts. The presence of cisplatin would bend the DNA duplexes by 95^{o} and thus the toxicity to DNA, although it is not sufficiently toxic to all cancers such as breast, prostate and colon. With similar leaving groups,

transplatin, carboplatin etc. could deliver similar Auger dose under the beam to tumor cells with much reduced chemo side effects to normal tissues beyond the coverage of the beamed radiation. Trans (cross)-platin, for example, would have much reduced cytotoxicity. By inducing the platinum atoms to initiate the soft Auger electrons *in Situ*, regardless cis or trans or carbo, the platinum could deliver the cellular modification for senescence at the molecular level and such a procedure forms a novel mode of cancer therapies whose side effects could be dramatically reduced. Using certain simple monochromatic X-ray equipment to initiate the mega Gy of soft Auger electrons *in Situ* will be explained in Section 2 below.

2. End Window Transmission X-ray Tube with Highly Efficient Line-Emissions [4,5]

Being six years older than Einstein, Coolidge designed his X-ray tube a century ago without engaging relativistic electron dynamics. At one hundred volts, electrons already reach 2% the speed of light, therefore most e-beams in an X-ray tube undergoing bremstrahlung (or brem, the slow down radiation) is really quite relativistic where the brem dipole trajectory moves from 90^o of the e-beam path to become parallel to the e-beam (Figure 2.1).

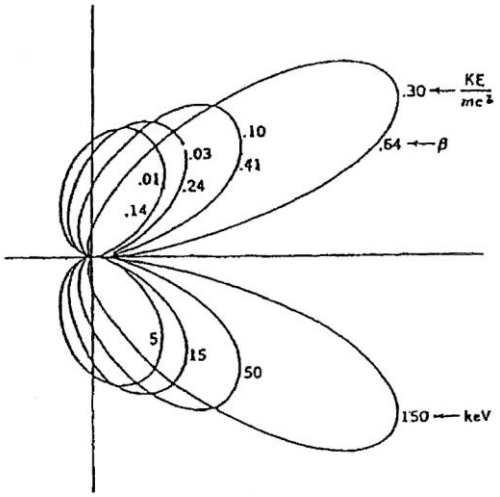

Figure 2.1

Bremstrahlung Dipole Trajectories Under Relativistic Transform, Moving From 90^o of the e-beam Path to Lean Forward and Become Parallel to the e-beam Path.

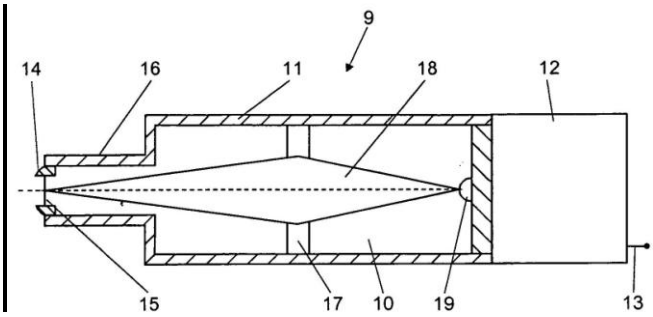

Figure 2.2

The e-beam in a Transmission x-ray tube with 10, vacuum; 11, tube enclosure; 12, Thermal Management; 13, Anode Ground; 14, Cathode Potential; 15; Filament Power; 16, Cathode Cage; 17, e-beam Focusing; 18, e-beam Trajectory; 19, e-beam/X-ray Focal Spot at the End-Window Transmission Plate

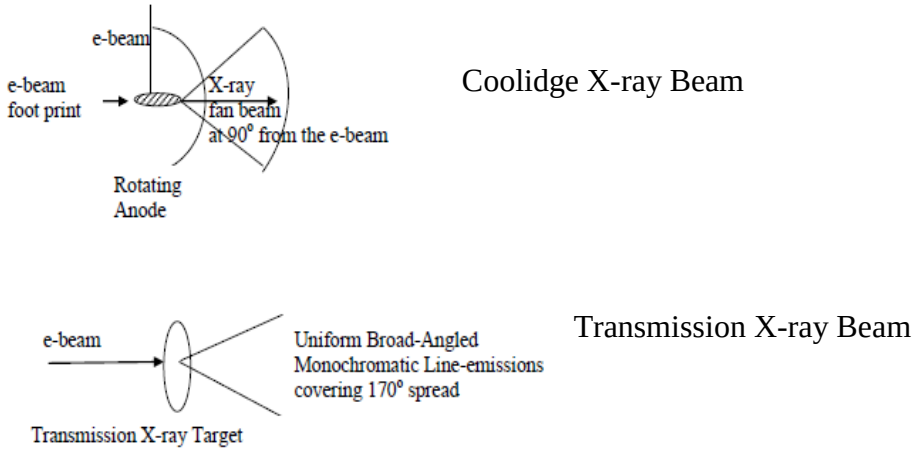

Figure 2.3 Coolidge Brem X-ray Fan Beam and Transmission X-ray Cone Beam Trajectories

As a result, through the transmission X-ray target (Figure 2.2), the X-ray tube could harvest a much larger fraction of X-rays by integrating the brem photons over all the azimuth angles and obtain a much brighter and uniform X-ray fluence. Figure 2.3 compares the X-ray beams from the transmission target and from the Coolidge tube. More importantly, using a transmission target with typically a thin film attached to a Be end-window, the thin target film also serves a filter function to screen out low energy photons and reduces the skin dose as well as transforms most high energy brems to fluorescent line-emissions characteristic to the target material(s).

Figures 2.4 show line-emissions of transmission Moly and Ag thin film targets. Resolution of the line-width shown in the Figures are mostly the noise level of the X-ray detector while the intrinsic line-widths δE have been measured by the Oak Ridge group with E/δE ≅ 3,690 to yield the Width δE to be approximately 6eV [6].

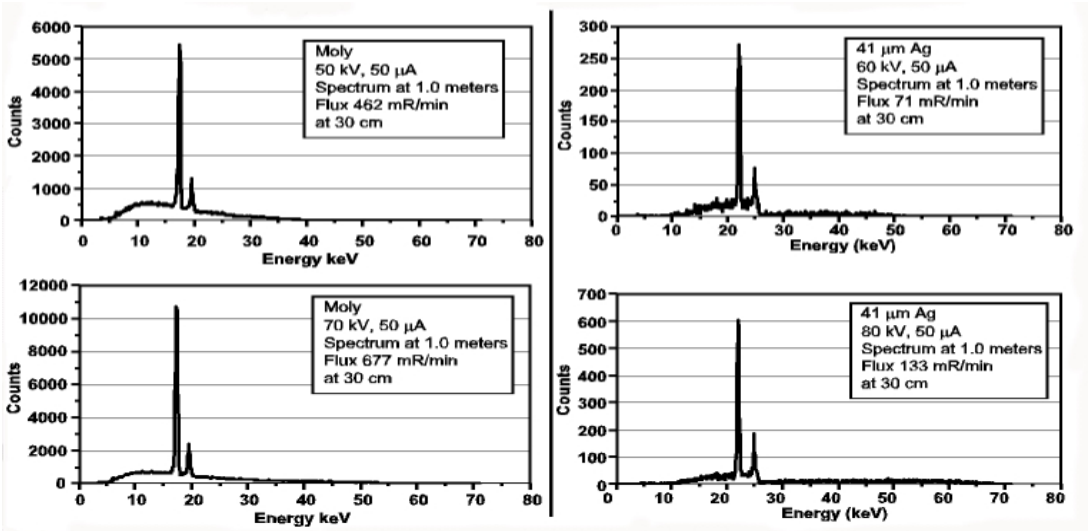

Figure 2.4 Some Characteristic Line-emission Spectrum

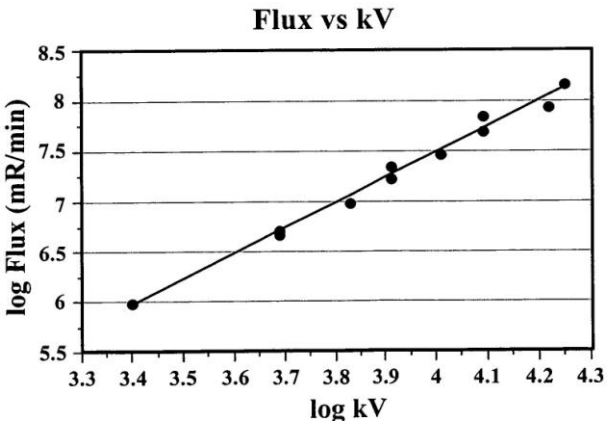

Figure 2.5

Transmission Tube Brightness, Mostly in Line-emissions, increases with kVp follows the power relationship of $kVp^{2.1}$ due to the relativistic transform while the Coolidge tube harvesting the beam at 90^{o} increases to $kVp^{1.7}$

Also note the kVp could be increased several folds with virtually no change in the emission spectrum in the tube using a transmission X-ray target whose brightness increases to the $kVp^{2.1}$ (Figures 2.4 and 2.5), as compared to the conventional Coolidge tube being proportional to $kVp^{1.7}$ with a shifted photon spectrum. The transmission target emission angle whose total X-ray fluence, mostly in line-emission, could be 250 times that of the Coolidge tube with kVp reaching 100kV. Most importantly, by making use of a greatly enhanced X-ray generating efficiency, the thermal load of a medical imaging unit such as mammography operating at 100kV without a spectrum shift, can be reduced from 6kW to under 100 Watts [5], for example, thus providing the X-ray tube to deliver a sharper focal spot with much improved line-pair formation in the imager.

Thermal Management of a Mammography Tube Using Phase Contrast

A conventional X-ray tube for mammography consumes 4.5-6 kilowatts, and calls for a Coolidge tube with a rotational anode in order to spread the thermal load from a single spot to the edge area of a spinning anode disc. By using the line-emissions of Ag at 22.1KeV, for example, the detector pixel would receive ~50% of the X-ray fluence instead of 5% so that the tube brightness can be reduced by an order of magnitude with dimming the detector fluence while the tissue dose is reduced by a factor of 19. Additionally, as shown in Fig. 2.5 where the kVp of the tube can be increased from 25 to 80 or 100kV without altering much of the X-ray spectrum in a transmission X-ray tube that gains the tube efficiency by $(80/25)^{2.1}$ =11.5, or a gain of another order of magnitude. Combining these two orders of magnitude gains, the thermal load of 6.5 kilowatts reduces to a load below 100 watts, which can easily be managed in a stationary anode with a sharp focal spot well below 100μm without active cooling, or at 40-50μm with active air cooling to the tube anode. With an enhanced X-ray generation efficiency and thus a simplified thermal management need, the transmission X-ray tube with mostly line-emissions to induce low energy Auger electrons to deliver the mega-Gy *in Situ* dose could indeed be a powerful therapeutic tool for molecular therapy at low cost.

References

[1] Auger Therapy www. Wikipedia

[2] Wang, CG, US 8,278,315 B2; 2012.

[3] Hannon, Michael J. “Metal-based Anticancer Drugs: From a past anchored in platinum chemistry to a post-genomic future of diverse chemistry and biology”, Pure Appl. Chem. Vol.79, No. 12 pp 2243-2261, 2007

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[6] Krause M.O. and Oliver J.H., Natural Width of Atomic K and L Levels, Kα X-ray Lines and Several KLL Auger Lines, J. Phys. Chem. Ref. Data 8,329 ;1979