Nanodynamics 88
34 East 29th Street, New York, NY 10016
Tel: 212-686-0759; Fax: 212-686-1479

Auger Therapy

1. What is Auger Therapy

Auger Therapy (AT) makes use of a very high dose [1] of ionizing radiation *in situ* that provides molecular modifications at an atomic scale. AT differs from the conventional radiation therapy in several aspects; it does not necessarily rely upon radioactive nuclei to cause cellular radiation damage at a cellular dimension, nor does it engage multiple external pencil-beams from different directions in order to zero-in to deliver a dose to the targeted area with reduced dose outside the targeted tissue/organ locations. Instead, the *in situ* delivery of a very high dose at the molecular level using AT aims for *in situ* molecular modifications involving molecular breakages and molecular re-arrangements such as a change of stacking structures as well as cellular metabolic functions related to the said molecule structures.

The high Auger dose [2] could be initiated by the inner shell ionization of a particular atom, leading to the "Auger cascade" to provide multiple low energy electrons, the Auger electrons, temporarily leaving its host atom. As low energy electrons have very short range in tissue or water, the Auger electrons would deposit all their energy in an atomic scale from the Auger event. By integrating energies from the Auger electrons over their nanometer (nm) range, and extending the nm scale into the cm^3 size as the radiation dose is conventionally calculated, the Auger dose would enter the 10^6 Gray range. Note that since most cellular apparatus are well beyond the Auger range at the nm scale, the micro-sized cell would generally function with no effect from the mega-Gray event except for it to occur at certain strategic cellular locations. To select and take advantage of the extremely localized *in situ* molecular modifications are therefore, the heart of Auger Therapy [3].

Auger electrons and Auger cascade were named in honor of the French physicist Pierre Victor Auger who traced charged cosmic ray trajectories in a cloud chamber. At the end of each ionizing particle traces, there always appears a concentrated formation of dense clouds called "delta rays", where the particle movements become randomized and deposit higher and higher kinetic energy per unit length until all the particle energy is exhausted.

For a moderately heavy atom with dozens of electrons, an inner shell ionization would lead to the filling of the said inner hole by an electron in the next shell level with very high probability (a L-electron to fill in a K-hole, for example), whose transition energy (L/K transition) will be absorbed by the neighboring electron (another L-electron) which will use the said transition energy to leave the atom as a low energy electron, the ionizing Auger electron.

Having one electron filling the inner hole and another electron leaving the atom, they leave behind two holes, which in turn, again with very high probability, are filled by two electrons in the next level whose transition energies would again be absorbed to eject two neighboring electrons to yield two more Auger electrons, etc. so that a cascade would result. That is, a single

Nanodynamics 88
34 East 29th Street, New York, NY 10016
Tel: 212-686-0759; Fax: 212-686-1479

inner shell ionization leads to, in short order, 1, 2, 4…etc. a cascading group of low energy Auger electrons, resulting with a mega-Gray dose *in situ* in a tissue or liquid medium.

2. Auger Dose Evaluation

The electron energy in a vacuum can be measured accurately by using an electron detector housed in a Faraday cage, for example, where the bias placed on the cage will accurately define the particle energy reaching the detector. The range of low energy electrons in tissue or water, particularly those electrons at the nm scale, however, cannot easily be measured and must be inferred because low energy electrons are easily scattered in very large angles and will travel in a zigzag path whose termination distance must be considered statistically and from differential measurements of higher energy electrons at a much higher range. 20eV electron, in water, for example, could have a range of 20nm for 10^3 Gray or 5nm for $10^{4.7}$ Gray, and for a group of 9-12 Auger electrons with energies at 12-18eV in water, including the effect of water ionization at approximately 10eV, an estimate of 10^6 Gray is probably sufficiently accurate. Figure 1 shows the simulated dose calculation in water for a single electron using Monte Carlo random walk [4] that gives up to 0.1 Mega-Grays; therefore for a moderately heavy atom to yield a dozen or more Auger electrons from its inner shell ionization, the Auger dose becomes 10^6 Gray per event.

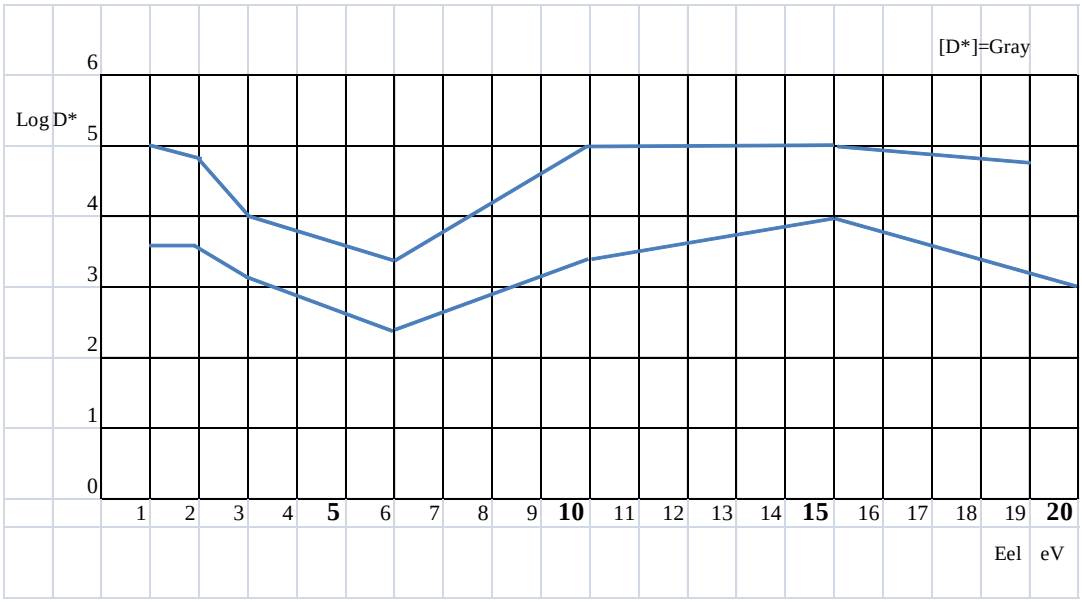


Figure 1, the Simulated Radiation Dose of a Single Electron in Water, where the Ionization Energy of Water at ~10eV shows a Resonant Enhancement in Dose. The Upper and Lower Curve stand for the Short and Long Limiting Ranges Respectively. Note that in vacuum, the Kinetic energy $\frac{1}{2}m_e v^2$ =1eV implies an electron velocity of 6×10^7 cm/sec, or 0.2% of the speed of light.

3. Candiates of Molecular Modifications with *in situ* Auger Dose

With a very large localized dose *in situ* for molecular modifications, the most obvious target molecule is the DNA duplex where the two complementary strands are separated by only a few nm. Atoms form the DNA duplex, however, are light elements with only a few electrons each and even if they could be induced by a photon beam to deliver the Auger electrons, the said photons at under 1,000eV will be too soft to penetrate any range of tissue thickness to be useful for therapy. Mid-ranged or heavy atoms, from Bromine to Platinum for example, that could be induced by sufficiently hard X-ray photons to generate enough electrons to provide many low energy charges in an Auger cascade, will be considered in several different therapeutic considerations.

3.1 Auger Electrons from Br for the Disruption of a Herpes-Specific Gene Expression

When a normal tissue/cell becomes transformed and replicates non-stop, many unusual genes, including sometimes viral materials such as the Herpes genes that are not expressed normally, becomes expressed with certain viral-specific functions.

The molecules under consideration to disrupt the Herpes gene is BrdC, where the Br replaces a methyl (CH_3) where they have almost exactly the same ionic radius and sit normally at the 5^{th} position for BrdU, which has an oxygen at top. BrdC could, therefore, be oxided and be used as BrdU. But prior to become oxide, BrdC could neither be used as dC or dU in mammalian cells except for the Herpes gene that could incorporate the BrdC as given. Next, the Bromine atom is made in transmutation from the element Arsenic with the addition of an Alfa particle in an ion-accelerator to form the ^{77}Br with a half-life of 57 hours from its K-electron being captured by a proton from an unstable nucleus and creates a K-hole in Br, leading to Bromine's Auger cascade [3] and disrupting the Herpes gene without killing the cell.

This experiment was carried out at Sloan-Kettering by Drs. Lawrance Helson and CG Wang [5] in the 1970s using 10 different neuroblastoma cell lines, from which two lines were successful in terminating the cell replication with ^{77}Br *in vitro* and the experiments were followed with a group of nude mice with tumor implants.

The *in vivo* experiments of mice, however, were complicated by the fact that mice's liver which would cleave off the sugar component of BrdC that renders both the mammalian and Herpes genes to incorporate the ^{77}Br-containing base with no distinction between them. Nevertheless, the Auger dose with ^{77}BrdC did disrupt the Herpes-specific gene for several transformed cell lines.

3.2 Auger Dose Aiming for Lysosome Using Rose Bengal [3]

Food color Red #95, Rose Bengal, can be ingested with minimal toxicity. The red molecules contain 4 Iodine atoms each and when diffused into cells, particular into those leaky transformed cells, they are quickly sent to/absorbed by the lysosomes attached at the goggi complex.

Lysosomes are very small sacks of hydrolytic enzymes in the cytoplasm at pH5. They were discovered by Christian deDuve using centrifugation to separate the cellular components [6].

In normal cellular functions, lysosomes together with proteosomes would digest a great variety of unwelcomed or discarded cellular components or molecules. With Rose Bengal distributed in the lysosome sac, the Auger dose induced by the inner shell ionization of Iodine would disrupt the acidic sacs and alter the pH of the cytoplasm, making it a localized chemotherapy [7].

3.3 Auger Dose Aiming for DNA Using Cis-Platinum [8]

The *in situ* Auger dose could be induced by a beam of energetic X-ray photons aiming for atoms such as platinum (Pt). The usual DNA is composed of elements too light to be induced by therapeutic X-rays for inner shell ionization, and among the chemotherapy agents, the Pt in Cis-Platinum is sufficiently heavy to provide either the K or L shell ionization for the useful Auger cascade with *in situ* Auger dose for therapy.

With a high *in situ* Auger dose, the use of chemo agents could be reduced, by an order of magnitude for example, and upon the irradiation of X-rays aiming for the element Pt to yield a localized Auger dose, the irradiated tissue/organ would exclusively receive the full therapeutic effect for a desired *in situ* chemo treatment [9].

3.4 Auger Dose for Localized Disruption Using Gadolium for Oncology and for Deaggregation of Amyloid-β

Gadolium (Gd) has the highest diamagnetic moment in the periodic table and has been broadly utilized in MRI as a contrast agent. For cancer metastasis, for example, the presence of Gd-compound in MRI from a leaky neovasculature has become the gold-standard for metastasic evaluations [10].

At a nm scale, the *in situ* AT could provide molecular modifications. But at a cellular dimension of microns, the enhanced Auger dose could increase the irradiating X-ray dose by only a factor of 2 or 3. Having such an enhancement factor, nevertheless, it enables a convenient mode of radiation that the X-ray beam can be used as a complement to surgical procedure to “mop-up” some local area/tissues without undergoing the full high energy gamma beams from various angles.

Gd is sufficiently heavy to be used for AT, and it can be attached to a variety of diagnostic molecules with high affinity to intercalate into the Amyloid-β of the Alzheimer's plaque [11,12]. Photons reaching the K-absorption edge of Gd can be delivered by the Thulim (Tm) K-emissions using a transmission X-ray tube with a Tm target. That is, the Tm-based X-ray tube would not only enhance the X-ray scattering cross-section with Gd embedded in the target location/region by an enhancement factor of a few on the micron-sized scale, but also deliver the 10^6 Gray *in situ* to perform molecular modification such as de-aggregation of the Amyloid-β of Alzheimer's plaques [13]. Figure 2 [14] outlines the formation of mis-folded protein to the plaque material.

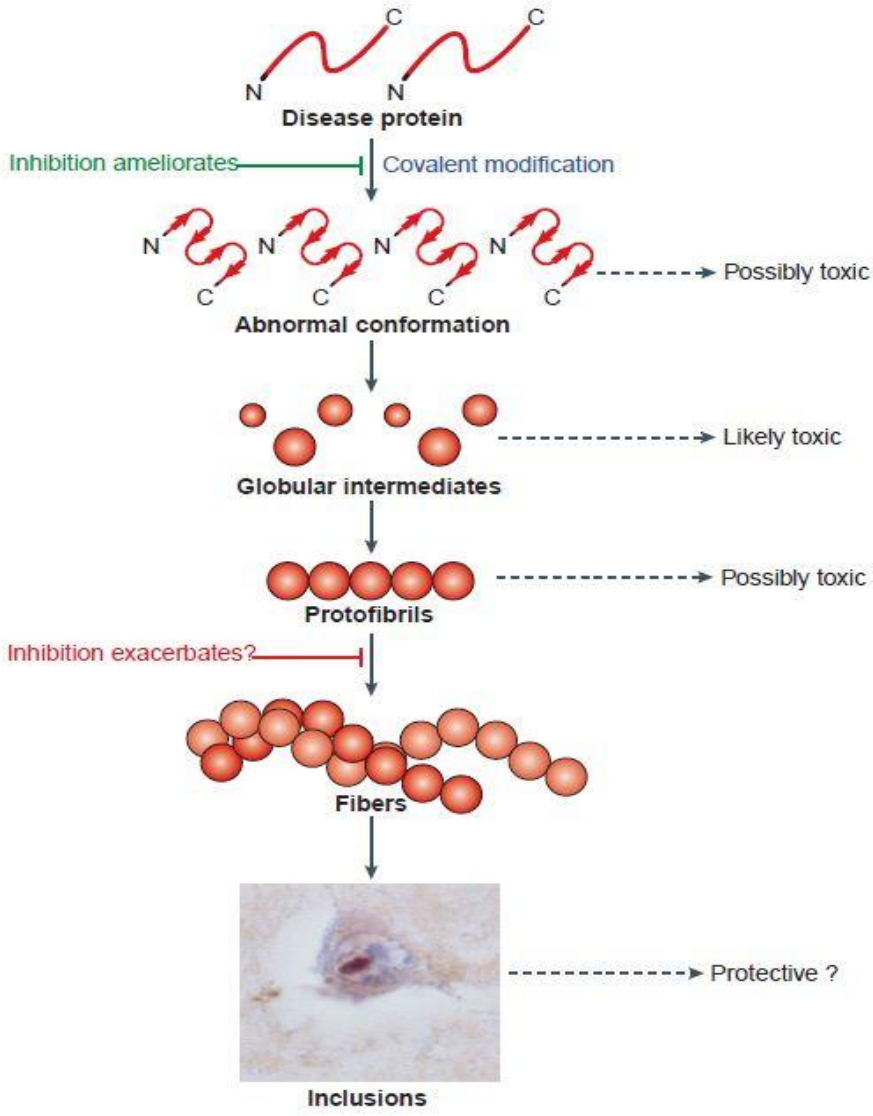


Figure 2. Plaque Formation from Mis-folded Protein

4. Monochromatic X-rays to induce Inner Shell Ionization

4.1 X-ray Tube with Transmission Target for Line-Emissions

Monochromatic X-rays can be channeled from synchrotron radiation, obtained from Coolidge X-ray tubes with extensive filtering, or from the preferred transmission X-ray tubes.

To induce an inner shell ionization with resonant scattering from a moderately heavy atom with dozens of electrons, the X-ray photon energy must be 30kV or higher in order to be effective to penetrate tissues for therapeutic applications. Synchrotron radiation is extremely bright and monochromatic without thermal scattering loss , but its brightness falls off at the 4^{th} power of the photon energy, and at 15-20 kV or higher, a low cost X-ray tube with a Moly target for example, could deliver as much X-ray fluence as that of a typical moderately-sized synchrotron instrument. In fact, the Coolidge X-ray tube becomes bright by $(kVp)^{1.7}$ while the synchrotron brightness goes like $(kV)^{-4}$, implying that it is generally not useful for desired Auger Therapy.

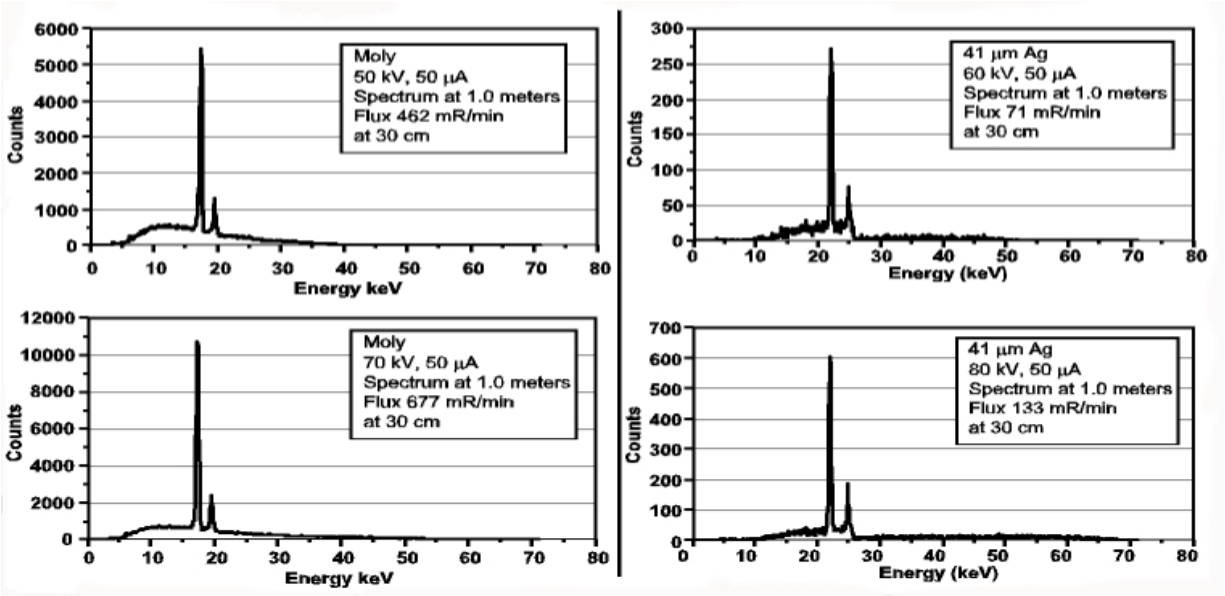
Coolidge X-ray tubes become brighter at higher energies, but by using external filters to haverst the useful photons without having the tissue to be exposed to unnecessary skin dose, the X-ray tube fluence must typically reduce by two orders or more in brightness, which is not an ideal case for therapy applications. This leaves the unique X-ray tube with end-window transmission targets [15].

In a transmission X-ray target, the X-rays are harvested along the direction of the e-beam path, in contrast to the conventional Coolidge tube where the X-rays from a solid target are collected mostly at 90^o from the e-beam path. The said X-ray beam has a sharp cut-off blocked by the target material at angles much beyond 90^o, and becomes much softer at angles below 90^o. As a result, the useful X-ray beam from a typical Coolidge tube is only $12\text{-}14^o$, although such a narrow cone could be extended along the surface of the solid target to result with a fan-beam that is commonly employed for body-slicing in computed tomographic (CT) imaging.

To harvest the X-ray fluence at 90^o from the e-beam path is indeed an optimal position in brightness without relativistic transform. Being six years older than Einstein, Coolidge at the turn of the 20^{th} century did not engage the proper electron dynamics with his design, the hundred years old patented X-ray tube including the rotational anode design for heat spread for higher thermal load. With relativistic transform, the bremsstrahlung (German word for slow down radiation, or brem) trajectories become forward leaning, moving along the e-beam direction, and if the X-ray fluence is collected from the transmission target in the forward direction and integrated over the azimuth angles, the X-ray fluence could typically be several hundred fold enhanced as compared to the Coolidge tube. More importantly, the e-beam range in an X-ray target material is only a few microns, so that for a 30μm thick transmission X-ray target, most of the target thickness would function as a filter that not only absorbs the very low energy photons,

but also transfers high energy photons into the fluorescent K or L-lines characteristic to the target element. In addition, the monochromatic line-emissions are emitted from the same refined X-ray focal point. Figure 4.1 demonstrates the K-line emissions of Moly and Silver targets, showing that the transmission target would deliver mostly bright, monochromatic X-rays from the small X-ray focal point defined by the e-beam focus.

Figure 4.1 Transmission X-ray Tube Spectrums with Moly and Ag Targets [16]



4.2 Transmission Tube Structure

By mixing the function of e-beam target with X-ray filtering, the transmission tube is different from the conventional Coolidge X-ray tube in several structured designs.

For a Coolidge tube, the filament for e-beam is at ground potential so that it can readily use a tungsten hair-pin to heat with several Amps of current. For a transmission target, the target must be grounded and the e-beam filament becomes negatively biased for the kVp, from which the filament current of several Amps cannot readily be supplied from a high voltage cable. As a result, the X-ray transmission tube and its high voltage power supply are integrated in a single unit in order to avoid the use of a massive high voltage cable as shown in Figure 4.2.

The transmission X-ray tube could deliver the X-ray beam far more efficiently than one using a solid e-beam target. Nevertheless, the thin target sheet has limited thermal capacity so that the target sheet must be attached to a thicker, thermally conductive material that is highly transparent to X-rays. Be of a few mm thick is therefore used for the end-window material that conducts the heat, seals the vacuum and positions the target layer.

Nanodynamics 88
34 East 29th Street, New York, NY 10016
Tel: 212-686-0759; Fax: 212-686-1479

The e-beam target layer could also be formed with a stack of different materials with each having a different set of line-emissions and allow the e-beam to be electronically switched to reach the desired layer for the preferred line-emissions. This line-emission with an electronically tunable feature could be very useful for image manipulation.

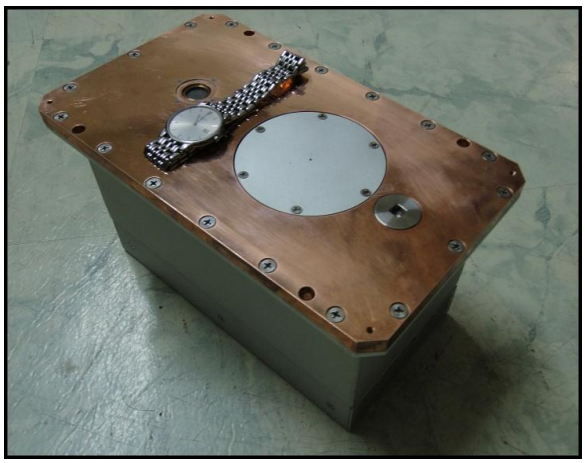


Figure 4.2, HV Power supply Integrated with the Transmission X-ray Tube. While this is a lower power unit than the proposed X-ray generator for AT, they are all small and portable.

References

[1] Kereiakes, JG, Rao, DV, Sastry, KSR, Howell, RW. Auger Electron Dosimetry. AAPM Report No. 37, January 1993.

[2] Persson, L. The Auger Electron Effect in Radiation Dosimetry – A Review. Swedish Radiation Protection Institute, S-17116 Stockholm, Sweden.

[3] Sastry, KSR. Biological effects of Auger emitter iodine-125. A review. Report No. 1 of AAPM Nuclear medicine Task Group No. 6. Med. Phys. 19(6), 1361-1383, 1992.

[4] J. Messungnoenab et.al, Radiation Research 1 58, 657-660; 2002

[5] Wang, CG and Helson, Lawrence, unpublished work; 1970s

[6] de Duve, C. The Lysosome turns 50. Nat. Cell. Biiol. 7(9): 847-849, 2005.

[7] Wang, CG and Helson, Lawrence, US Patent 7,981,928 B2; 2011

[8] Long, DF, Repta, AJ. Displatin: Chemistry, Distribution and Biotransformation. Biopharmaceutics and Drug Disposition. 2:1-16, 1981.

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

[10] Wilms, G., Marchal, G., Demaerel, PH, Van Hecke, P., Baert, AL. Gadolinium-enhanced MRI of intracranial lesions. A review of indications and results. Clin. Imaging, 15(3): 153-165, 1991.

[11] Ikonomovic MD. Et. al. Post-mortem correlates of in vivo PiAB-PET amyloid imaging in a typical case of Alzheimer's Disease. Brain 131: 1630-1645, 2008.

[12] New Imaging Agent Being Tested for Early Detection of Alzheimer's. Published online, Diagnostic Imaging. Eli Lilly compound Flutemetamol.

[13] Ledford, Heidi. Harmless Prion protein linked to Alzheimer's disease. Published Online 25-Feb-2009; Nature: doi:10.1038/news.2009.121.

[14] CA Ross and MA Poirier, Nature Medicine "Protein Aggregate and Neurodegenerative Diseases" published online July 2004; doi: 10.1038/nm1066

[15] Wang, CG, U.S. Patent 7,180,981B2; 2007.

[16] Wang, CG and Thomas Vullo, US Patent 7,430,276B2; 2008