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Tunable, Monochromatic X-Rays: An Enabling Technology for Molecular/Cellular Imaging and Therapy

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Abstract Pulsed, tunable, monochromatic X-rays hold great potential as a cellular and molecular probe. These beams can be tuned to the binding energy of orbital electrons in atoms, making them extremely useful in diagnostic k-edge imaging and Auger cascade radiotherapy. Their wide tunability makes them ideal for the performance of various techniques as disparate as protein crystallography and three-dimensional, compressionless, monochromatic mammography. Since only the frequency best suited to the task at hand is used, radiation exposure to patients or animals is exceedingly low when compared to standard X-ray techniques. J. Cell. Biochem. 90: 502–508, 2003.

Key words: monochromatic X-rays; k-edge; Auger cascade; crystallography; mammography

In the 108 years since Roentgen's discovery of X-rays, use of these beams in the diagnostic and therapeutic arenas has developed into a fine art. One has only to think of multislice Computed Tomography (CT) with three-dimensional reconstruction used everyday in most hospitals to confirm this. However, such modalities still rely on "brute force" X-ray production in tubes that rely on converting 99% of their energy into heat and the remaining 1% into braking radiation (Brehmstralung) to produce "white"/polychromatic X-rays. These, unfortunately, deliver high radiation doses to the patient and create significant scatter as they penetrate the tissues. These "white X-rays" are similar, in many respects, to the admixture of many different visible colors from a standard light bulb, perceived as white light by the eye.

The invention of lasers with their intense narrow bandwidth emissions has led to a revolution in the ways that we use light in our everyday lives to analyze and cut materials, store and display data, transmit information, perform surgery, and so on.

In like manner, development of the methodology to produce intense beams of tunable, narrow bandwidth X-rays from a compact source could act as an enabling force that would open new doors in diagnostic imaging, therapeutics, and biomedical research.

To that end, a development project begun in 1987 at the Vanderbilt University Medical Free Electron Laser (MFEL) Center sought to produce such X-ray beams using the phenomenon of Inverse Compton Scattering (Fig. 1). Late in 1998, our group was successful in producing pulsed, tunable, monochromatic X-rays using the free electron laser as a source of both high-energy electrons and intense infrared (IR) laser light. Focusing these two beams to a diameter of 100 microns and colliding them head-on yielded tunable, monochromatic X-rays in the 14–18 keV range [Carroll et al., 1990, 1999].

However, for use in a clinical or research setting, even this technique left much to be desired. The FEL, for example, is approximately 30 m long, and creates an exceptionally intense radiation environment while running, necessitating its installation in a heavily shielded vault consisting of over 2 m of concrete. Since the original monochromatic X-ray beamline yielded only about 176 X-ray photons/3 ps micropulse of electrons, creation of a useful beam for imaging required millions of electron pulses. In addition, this technique mandated deflection

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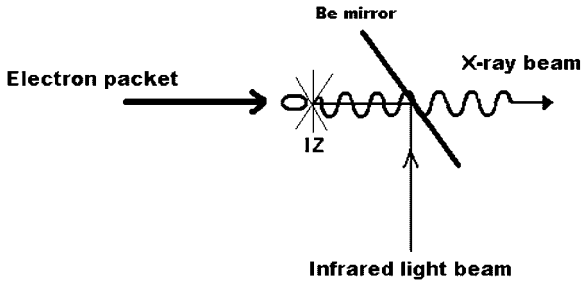

Fig. 1. Inverse Compton Scattering entails the head-on collision of an energetic packet of electrons and an intense laser pulse (in this case infrared light reflected off of a beryllium mirror) at a point called the interaction zone (IZ). The light photons are scattered off of the electrons gaining energy and shortening their wavelength to the X-ray region of the spectrum. Since the electron energy is tunable, the X-rays are tunable. Since the light waves were almost all at the same frequency, the X-rays coming out are almost all at the same wavelength. The X-rays are scattered in the same direction as the electrons were traveling, and exit the beamline through the beryllium mirror and a beryllium window.

of the X-rays off of mosaic pyrolytic graphite crystals at a large angle to bring them to a shirtsleeves environment where they could be used on a patient, animal, or sample. Over 95% of the X-ray flux produced was lost in this fashion. As the electron beam was optimized for maximal X-ray production, IR photon output spiraled downward hampering FEL performance. It was obvious that a new design was needed.

In April 2001, after 2 years of design and engineering, a new prototype device was completed and commissioned at the MFEL Center but used a configuration that was not that of an FEL. This machine uses a linear accelerator operating in what we call the "single pulse" mode and a tabletop terawatt IR laser to provide the counter propagated beams. It delivers 10^{10} X-ray photons/8 ps pulse throughout its tunable 12–50 keV range at anywhere from a 1–10% bandwidth in a conebeam area geometry. A single electron pulse is accelerated when the terawatt laser fires, allowing operation of the entire machine in a shirtsleeves environment containing unbadged personnel. This machine has been operational for 1½ years and is used for monochromatic imaging of phantoms and mice, and for feasibility studies and applications research [Carroll et al., 2003]. The versatility of the monochromatic X-rays produced has unlocked a treasure chest of possibilities in molecular imaging and cellular manipulation. Among these are k-edge imaging, Auger cascade radiotherapy, and monochromatic 3-D compressionless mammography to name a few.

k-EDGE IMAGING

The manner in which an X-ray beam interacts with matter, of course, depends upon the chemical composition of the matter. In complex tissues, such interactions are weighted proportionally toward heavier or lighter elements. Although the body is predominantly made up of hydrogen, oxygen, carbon, and nitrogen, the presence of tightly packed nuclear chromatin in highly cellular tumors, for example, would shift a tissues' composition away from just water, and therefore change it's mass attenuation (i.e., the less hydrogen and oxygen present and the more phosphorous, nitrogen, and carbon that replace them in the more plentiful nuclei, the greater the stopping power of the tissue). These effects have been seen in breast malignancies without the addition of any contrast agents, and can be seen in normal organs such as the thyroid [Johns and Yaffe, 1987].

Transgenic mouse models expressing either the *neu* proto-oncogene or transforming growth factor (TGF-α) in the mammary epithelium develop spontaneous focal mammary tumors that occur over long latency. These models offer a test bed in which to follow changes in linear attenuation of the tissues as the epithelial alterations occur over 6 months from glandular and ductal tissues that are normal, to those with clearly defined macroscopic hyperplasias or tumors. Tyrosine kinase inhibitors are being tested to halt or reverse these effects in the mammary tissues. These transgenic mice can be followed longitudinally over time with a monochromatic X-ray beam without the exceedingly high radiation doses now delivered in even one microCT exam [Arteaga et al., 2001].

The addition of other atomic species can significantly enhance k-edge effects, particularly as one tunes the incident radiation beam to target the k-edge of the element given. k-edge refers to the specific binding energy of the innermost or k-shell electron in the atom of interest. If, for example, iodine were introduced into a tissue by means of an iodine tagged tumor affinitive drug, one could detect its presence in rather small concentrations given a monochromatic beam tuned to 33.2 keV (the binding energy of its k-shell electron) and a good imaging detector (Fig. 2). The X-ray photon, in this case, matches

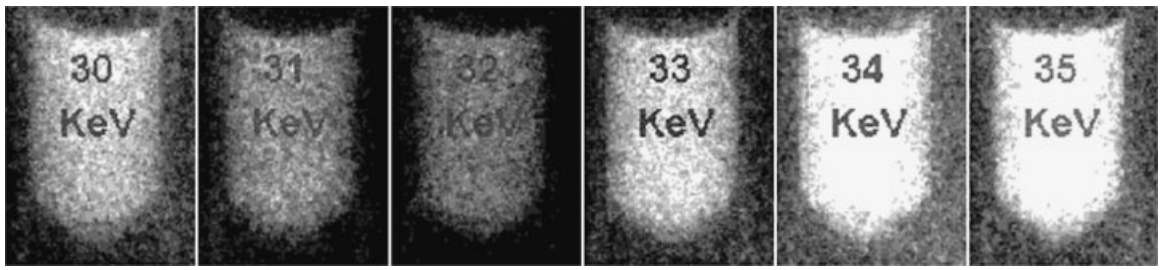

Fig. 2. A test tube containing an iodine solution with approximately 37.5 mg I/cc, was imaged with a monochromatic X-ray beam at progressively higher energies (1 keV steps). Absorption of the X-rays by the iodine initially decreases with increasing energy, as expected, until the k-edge of iodine (33.2 keV) is reached. Above that energy absorption increases markedly causing the iodine within the tube to ''light up'' revealing its presence.

the binding energy of that electron, and "knocks it" out of its orbit. The X-ray, having transferred its energy to the electron, is extinguished from the beam, thus revealing the presence of the iodine along the X-ray's original path.

A number of drugs are already under investigation for diagnostic use as molecular or cellular tags, and as contrast agents. Early experiments with new ideas for *diagnostic* agents have already begun in our laboratory. These are being performed with iodine containing COX-2 agents, Gd containing immunoliposomes, and PV-10 (iodinated rose Bengal)® (Provectus, Inc.). COX-2 protein is not expressed extensively in normal cells, but is expressed significantly in stomach, colon, pancreas, liver, lung, breast, and prostate malignancies [DuBois et al., 1996]. This makes COX-2 an attractive molecular target in research animals and potentially humans. Researchers at other institutions have done preliminary work on many other diagnostic drugs such as: hepatocyte selective iodinated triglycerides, which act as a negative contrast agent [Lee et al., 1997]; AgTPPS4, which is a porphyrin derivative that accumulates in vasculature around tumors [Young et al., 1998]; iodine containing micelles made from polymers [Torchilin et al., 1999]; Gd compound P 760, which slowly diffuses into the interstitium [Kroft et al., 1999]; gases such as Xe for airways and alveoli [Rubenstein et al., 1995]; perfluorocarbons which can be used as both liquids and gases; dextran-coated Fe oxide nanoparticles [Moore et al., 2000]; and hexanuclear transition metal cluster compounds [Mullan et al., 2000], to name a few. Certainly the currently available iodinated contrast agents used intravenously, intra-arterially and even intrathecally can be used at extremely low doses using monochromatic X-rays both at the 33.2 keV k-edge and, to even better advantage in certain portions of the body, such as the breast, in the 20–30 keV range. Marked reduction in the concentrations of contrast that can be visualized, opens the door to IV angiography using small intravenous injections, reducing the need for catheterization of the arterial system, thus improving safety, and patient acceptance [Ohtsuka et al., 1994; Dix, 1995; Dix et al., 2003].

Gadolinium containing MRI contrast agents are currently used in the angiography setting as a substitute for iodine in allergic individuals, but there is some controversy that it is less toxic than iodine in equally attenuating doses (0.5 mol/L Gd attenuates the same as 60–80 mg I/cc). This is partly due to the polychromatic beam that is used (70–90 KVP), which is not tuned to the k-edge of the gadolinium, markedly reducing its visibility. By tuning to the k-edge of the gadolinium atom (50.2 keV), one can use much less contrast, maintaining the k-edge effect, but the body is much more transparent to the X-ray beam than it would be at the k-edge of iodine, thereby also reducing the radiation dose to the patient.

Heavy elements do not necessarily need to be introduced exogenously into the body to take advantage of this k-edge effect. Some elements concentrate in tissues in certain diseases (e.g., in Wilson's disease, there is an abnormal over accumulation of Cu; in hemochromatosis, iron builds up in tissues, such as liver and lung; lead poisoning affects calcium deposition and resorption in the regions of rapid bone growth at epiphyses, etc.). These elements can be easily detected using tuned monochromatic X-ray beams.

Osteoporosis screening as currently practiced, is an example of chemical probing using different frequencies of X-rays. Few people think of this as X-ray probing of molecular composition of bone, but that is precisely what it is.

One need not be exactly tuned to the k-edge of an element to see a detectable effect. In fact, at low concentrations of heavy elements (e.g., iodine), one can discern tissue concentrations at and beyond micromolar levels within laboratory animals such as mice, when imaged far below the k-edge, due to the increased likelihood that lower energy X-ray photons will interact with heavier elements (more so than water) due to the photoelectric effect that is dominant in the 20–30 keV energy range.

The effect of inherent tissue changes with various pathological states and the addition of exogenous heavy elements into those tissues are not necessarily additive. Going to a higher X-ray energy to interact with the more tightly bound k-shell electron of a heavier atomic element will tend to obliterate the underlying effects seen inherently in tumors that are best imaged with lower energies and hence higher soft tissue contrast.

THERAPY

When the k-shell electron of iodine is knocked out of its orbit by tuning monochromatic X-rays to 33.2 keV, the ejected electron is replaced in the K orbit by an electron from the L orbit. As this electron drops from the L to the k-shell, it gives off a 28.3 keV characteristic photon. Likewise, the L-shell electron is then replaced by an electron from the M-shell. This in turn gives off a 4.3 keV photon. The N-shell follows the lead of the other shells and contributes an electron to the M giving off a 0.6 keV photon. As one could expect, adding up the energies of these various photons comes to 33.2 keV. These characteristic photons interact with the matter in their surrounding medium, traveling less then a few microns at most for the softer X-rays, but penetrating some distances for the more energetic ones. This entire process is known as an Auger cascade (Fig. 3).

A unique approach to targeted *therapy* is possible using an infusion of iodinated deoxyuridine (IUdR) into a patient. This allows the replacement of as much as 10% of the thymidine in the nuclear DNA of rapidly dividing cells. An external monochromatic beam may then

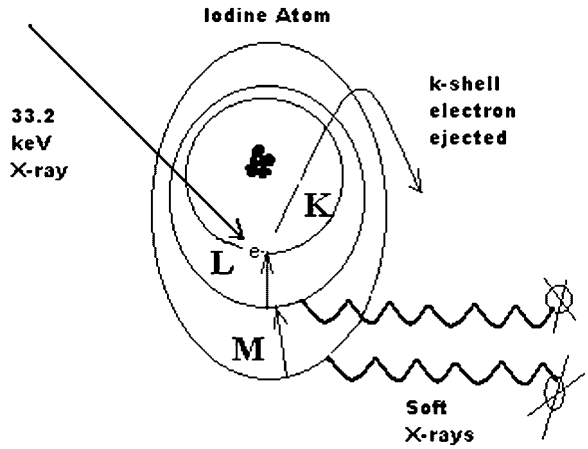

Fig. 3. Auger cascade. A 33.2 keV monochromatic X-ray knocks the K-shell electron out of its orbit around the nucleus extinguishing the X-ray photon. The ejected photoelectron interacts with surrounding tissues. Meanwhile, the L-shell and M-shell electrons fall into the next lowest orbit emitting soft X-rays in the process. These interact with the surrounding soft tissues as well. Cascades such as this can be quite damaging if they occur in very close proximity to DNA in the cell nucleus.

be used to displace the k-shell electron in the contained iodine, thereby creating an Auger cascade within the DNA, creating double-stranded breaks. One Auger event in the DNA of a cell is the equivalent of delivering 0.05 Gy (5R) to the cell [Kassis et al., 1987]. Significant reductions in the doses needed for radiotherapy could be achieved in this way. Monte Carlo calculations show a 25–50% reduction in dose needed, depending on depth of tumor and starting energy of the monochromatic beam. The inner shell (k-shell) ionization events are 4–8 times less frequent if one uses BUdR instead of IUdR. Pignol et al. [2003] have shown that the k-shell events are strongly tied to the photon spectrum of the beam or radionuclide used to knock the k-shell electron from its orbit and that the lower one can go in beam energy toward the k-shell binding energy the better it gets [Karnas et al., 1999].

It would seem intuitive that by using a slightly more energetic beam, more of the photons in that beam would survive passage through the overlying tissues to make it to a tumor at a given depth. It would then seem best to place heavier atomic species in the cell that have k-shell binding energies that would conform to these more energetic photons. Given this logic, gadolinium with a k-shell binding energy of 50.2 keV and now present in some current chemotherapeutic agents would seem

ideal. Unfortunately, the doses at which it is used clinically are not relevant for the Auger cascade phenomenon. One of the problems with using Gd-Tex, for example, as a radiosensitizer is that it winds up mainly in the mitochondria rather than in the DNA in the nucleus [Miller et al., 1999]. If one is given the choice of either creating free radicals randomly within a cell hoping to incapacitate various intracellular mechanisms or, alternatively, to create a double-stranded break in the DNA that will halt cell replication in its tracks, the choice requires little profound cogitation.

It would appear then that it is more advantageous to improve the effectiveness of radiosensitizers through optimizing irradiation depth and photon energy than to attempt forcing more of the drug into the cell through pharmacological manipulation.

In a similar vein, the combination of an adenovirus, a symporter gene, and prostate specific compounds can also be used therapeutically. While not containing the target atom itself, this combination, when given to mice, infects the prostate cells, altering cellular genetic makeup, imparting new capabilities to the cell enabling it to transport and concentrate sodium iodide, much like thyroid cells [Spitzweg et al., 2001; Cho et al., 2002]. While current experiments use radioactive iodine uptake and its disintegrations to then both diagnose and treat tumors, collateral damage may be expected both around the prostate cells themselves, but also in the thyroid gland, salivary glands, stomach and so forth where iodine may also accumulate. Use of non-radioactive iodine with an external beam tuned to the k-edge of the iodine could potentially spare these other organs, while still creating Auger cascades within the transformed cells to help in killing them.

A newer and somewhat elegant method of testing distribution of dose in tissues to learn more about the k-edge enhancements with Auger cascades is the use of aqueous polymer gels. These consist of tissue equivalent materials with radiosensitive monomers dispersed throughout the gel. The products of radiolysis (production of free radicals) cause the monomers to polymerize. The degree of polymerization depends directly upon radiation dose. When these gels are studied in a magnetic resonance imaging unit, the water relaxation times are shorter in the presence of polymers or macromolecules. These in essence act like self-developing three-dimensional photographic emulsions. If one were to seed "tumors" containing k-edge drugs into these gels, one could directly test the effectiveness and build up of radiation dose equivalency using IUdR and monochromatic radiation.

Where does molecular/cellular imaging eventually take one? While it is unlikely or even unnecessary that we will ever need to see only one cell or one metabolic event, imaging down to the cellular level is possible but the radiation burden is so high that it is impractical even with monochromatic X-rays. Fortunately, people are conglomerations of many cells. If we wish to use molecular or cellular imaging in every day clinical practice, we must not only explore the effectiveness of monochromatic X-rays in cell cultures or single cells but also determine whether or not we can see these effects at depth within the patient. This is going to require penetrating radiation of some sort, whether it is monochromatic X-rays, radio waves, gamma rays, or ultrasound. There are, of course, many trade offs in spatial resolution, detector efficiency, and the concentrations of materials that need to be present in the tissues for detectability by different modalities. Needless to say, one technique will not suffice for all situations. Multimodality approaches to understanding the molecular events at depth within a patient certainly need to be available to clinicians.

Any techniques that translate into the clinical arena must gain patient acceptance. Patients will not accept invasive or painful techniques. An example of this is the compression used in current day mammography. Compressionless examinations, use of oral drugs rather than intravenous drugs, and low radiation doses will all be high on the list of "musts." In three-dimensional, compressionless, monochromatic mammography, inherent differences in the linear attenuation of the cells in cancers [Carroll et al., 1994] will be much easier to detect without the overlap of structures within the breast that is currently problematic with 2-D images [Gordon and Sivaramakrishna, 1999]. This technique will produce an examination that is much more reproducible from year to year making better use of computer assisted diagnosis (CAD) techniques now showing promise. This could all be accomplished with a much lower radiation dose than that currently delivered [Boone, 1999; Kimme-Smith, 1999; Boone et al., 2001]. High spatial and contrast

resolution are needed if we are to use this type of molecular/cellular imaging to best advantage.

The pulsed, tunable, monochromatic X-ray machine currently used to perform applications research in phantoms and animals is capable of forming an image in 8 ps, but can do so only once every 300 s. Needless to say, if this paradigm is to be used in the clinical setting, a higher repetition rate machine will be needed to make these studies practical. Developments in laser technology are being incorporated into the machine design allowing it to be useful clinically in cancer diagnosis and treatment, calcium screening, coronary and lung perfusion studies with intravenous injections, and a whole host of other scenarios.

Of interest, is the fact that monochromatic X-ray beams produced by inverse Compton scattering are ideal for the performance of protein crystallography [Harteman et al., 2001]. With addition of a high repetition rate laser to one of these machines, crystallography in all of its forms can be performed outside of the synchrotron setting speeding up the determination of the three-dimensional structure of a subject protein. If one need not wait for months or weeks to get time on a synchrotron beamline to ascertain whether or not a protein crystal is useful for crystallography and will give a good diffraction pattern and yield the 3-D information needed, the tempo of drug discovery and structural proteomics could be significantly enhanced.

Pulsed, tunable, monochromatic X-rays have great potential as an enabling technology for diagnostic and therapeutic techniques that will be quite useful in the arenas of patient care, small animal research, and drug development [Carroll, 2002]. In these formative years, the rationale for how they are best used must rely on understanding the cellular and molecular mechanisms that they can easily probe. Merely seeing internal anatomy is not enough; we need to be able to remotely feel its texture, probe its chemistry, or delete it entirely if it is an unwanted intruder. First, we need to do no harm, so we must peek at the microscopic innards of our patients painlessly and as unobtrusively as possible. This type of X-ray probe holds promise that we must carefully nurture.

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