Program of Photonics and its Applications to Medicine

Professor T. Tajima, Norman Rostoker Chair Professor, University of California at Irvine

Abstract

We work on the Photo-Medical Physics Project to harness the revolutionary photonics technology (using ultra-fast high power lasers and transforming those to a tunable narrow-band x-ray beam) to extremely sensitive molecular medical imaging and low-dose targeted therapy as well as new technology of zeptosecond lasers. These techniques will introduce a theranostic approach with unprecedented contrast mechanisms for diagnostic imaging and highly selective treatment of tumors without collateral damage.

I. Introduction

Medical application of high energy photonics

The utilization of laser radically advances the diagnosis and therapy in a variety of medical conditions, including cancer. The introduction of femtosecond lasers, particularly intense lasers, in medicine is the frontier. UCI has been at the forefront already in medical applications of photonics at the optical regime (~1eV photons) such as LASIK in which Professor T. Juhasz and Professor R. Kurtz have pioneered in the femtosecond laser technology[1] for cataract laser surgery. Besides many other research groups, Beckman Laser Institute has also been at the forefront of the biophotonics research at UCI for diagnostic imaging and well as photonics based therapy.

Laser up till now in general has made revolutionary advances using optical (~1eV) photons to open up the frontier of atomic physics and chemistry and science and technologies of photonics, ushering in the Century of Photonics. However, thanks to the efforts of the pioneers some of whom are on this proposal, we learned how to boost the energy of the optical photons tens of thousands of times (> 10KeV), Fig.1.a. By so doing, laser has now entered as a most powerful tool into the subatomic fields. In this proposal we form a unique integration of UCI's leading talents in interdisciplinary laser breakthrough exploration into the subatomic regimes such as the nuclear photonics, in addition to the photonics applications in the optical regime.

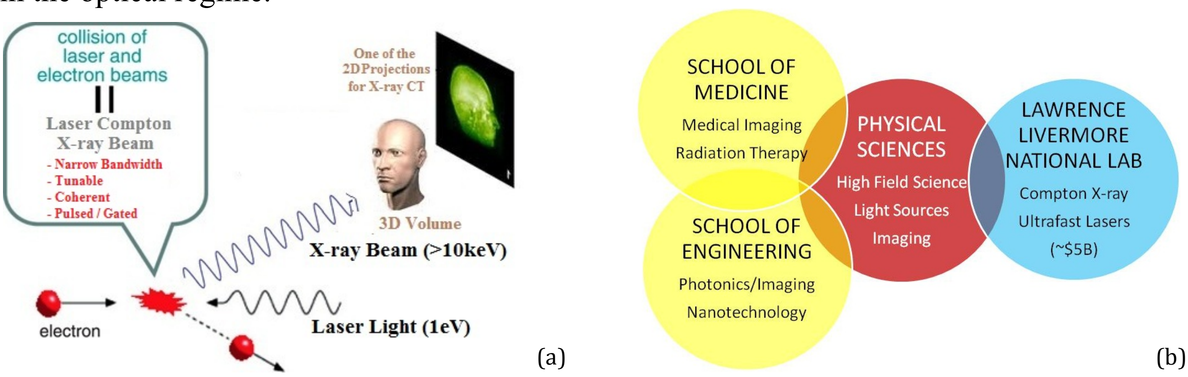

Figure 1. (a) Emerging Laser Compton technique: a low energy laser beam (~1eV) is transformed into an x-ray beam (>10keV) after backscattering off an electron beam. This interaction produces a narrow-bandwidth coherent X-ray beam. By changing the laser color or the energy of the electron beam, the energy of the X-ray can easily be tuned and gated (with cardiac cycle for example). None of these properties are attainable with conventional X-ray tubes. This ground-breaking technology has been limited with room-full of size equipment but our collaborators at LLNL shrunk it to a table-top version. Our vision is that in the long-run, these sources will be compact and replace the conventional x-ray tubes, therefore open a new generation of molecular medical imaging phase using X-rays. (b) The world-class integrated talents of three Schools of UCI and LLNL will contribute to this proposal that will also provide a fantastic educational platform for students and junior scientist.

We are collaborating with a world-class team of physicists, physicians, and engineers on this frontier field. Our aim is to cultivate the ground that addresses and advances this field in collaboration of our colleagues in School of Physical Sciences, School of Medicine, School of Engineering and Lawrence Livermore National Laboratory (LLNL, UC) (see Fig.1.b). Through this effort synergy of physics, chemistry, medicine, and engineering will get into a new height, depth, and breadth. Laser and its driven elevated technology will be the focus of the new cross current of medicine, physics, and engineering that enable all three to integrate with each other and impact the society.

As one of the specific examples, let us describe the development of nuclear photonics. A laser pulse backscattered off an electron beam is capable of generating tunable X-rays and gamma-rays (and other frequencies if so desired)[2]. The electron beam may be generated by the state-of-art rf X-band linac technology[3] (while it may also be generated by laser acceleration.[4] The latter method further compactifies the accelerator. This approach also provides an additional method of generating coherent X-rays via betatron radiation.[5]) In this proposal the culminating technical combination of the bright, high-fluxed linear accelerators and the efficient robust high-intensity laser is employed as the main X-ray light source for medical applications to advance the frontier of radiological diagnosis and radiotherapy of cancer. The history of laser Compton X-rays and γ-rays itself is long. For instance, the first large-flux GeV Compton γ-ray beam was generated at Spring-8 in 1990's at the advice of the Dr. Tajima.

In addition, we (Professor G. Mourou and T. Tajima) have started the new photonics technique that is based on single cycle optical laser compression technique combined with relativistic mirror on a surface of a metal to produce coherent single-cycled X-ray laser, which can drive ne particle and photon sources (Tajima and Mourou, 2014). Applications of this to medicine are many-fold. In a broadest sense this introduces the science in zeptoseconds.

Collaboration with LLNL: However, the cutting-edge technology for compact, highly efficient, mono-energetic, pencil-beams of X-rays by the laser Compton approach (Fig. 1.a) has been perfected[6] by Dr. C. Barty's group at LLNL, advancing the potential brilliance of X-rays by more than 6 orders of magnitude. These characteristics are a radical departure from the conventional anode technology used in the vast majority of medical X-ray procedures (see Table 1). [7]

Attribute	LLNL Picket Fence c-2013	LLNL T-REX c-2009	MXIS c-2007	Rotating Anode	Units
bandwidth	<0.5%	8%	10%	100%	ΔE/E
collimation	<0.5	1	2	524	mrad
source size	15	30	35	150	microns
average brilliance	~1E+13*	8.89E+10	3.60E+06	6.00E+07	ph/s/mm2/mrad2/0.1%BW
e-beam current	3.60E-03	5.00E-06	2.08E-09	100	mA
laser power	240	3	0.0036	n/a	W

Table 1. Recent evolution and characteristics of laser-Compton x-ray sources in contrast to the conventional rotating anode technology.

As is well known, LLNL is the world leader on energetic lasers with multibillion dollar research infrastructure. It is also worth noting that because of the revolutionary nature of this technology, the PI recommended this as the cornerstone of the proposed Extreme Light Infrastructure (now funded at the level of ~$1B) as Chair of the Scientific Advisory

Committee[8] of ELI in 2010, which now harbors ELI Nuclear Pillar's one of two light sources suitable for the nuclear relevant energies of MeV and beyond. Here in the current proposal we adopt it to the energies of medical relevance (< 50keV). Thus our project will be carried out in further collaboration between UCI and LLNL in marshaling this technology toward the medical diagnosis and therapy applications.

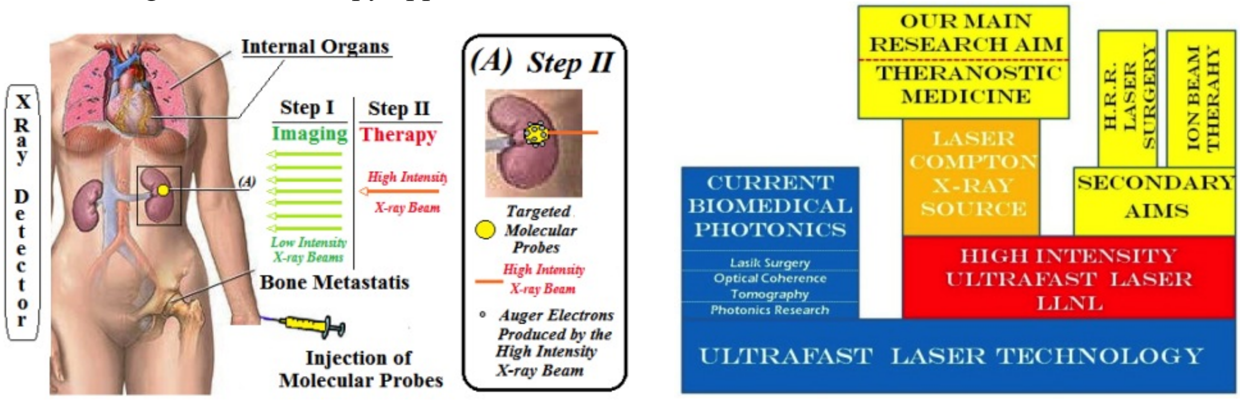

Figure 2. (a) Our main research area will be Theranostic: both diagnostic and therapy of diseased tissue using this novel technology. In summary, the disease targeting molecular probes will be injected to the patient and after they accumulate in the diseases tissue, imaging will be performed first using low energy X-ray beams. Once the targeted agent are localized using K-Edge imaging that provides superior contrast, high intensity beam will be focused only on the targeted agents. Auger electrons emitted by the targeted molecular probes that carries high-Z elements such as gold, iodine, gadolinium or platin will provide local targeted therapy. (b) The current biomedical photonics is based on the landscape of the ultrafast laser. Our collaborators at LBNL has ultra-intense laser technology that is the basis of Laser Compton X-ray Source. Although our main aim is to use this novel source for theranostic medicine, our secondary aim will be utilizing this technology for biophotonics applications such as laser surgery and for ion beam therapy in the future.

The applications of these X-rays and gamma-rays to medicine and pharmacology will be investigated. The tunability and spectral narrowness of the X-ray energy and the high degree of phase coherence allow us to create a new height in the high resolution X-ray diagnosis (such as the K-shell contrasting[9] and the phase contrast imaging[10]) of tissues and tumors. The X-ray pulse with a specific energy that matches the K-shell level is capable of producing a cascade of Auger electrons[11] that will induce local radiation dose and provide local of the targeted lesion. In this approach, a cancer-targeting agent is tagged with a high atomic weight element. After injection of the agent the diseased area determined by the diagnostic imaging is illuminated with a mono-energetic beam of X-rays tuned to an energy that is slightly above the k-edge absorption threshold of the tagged element. These photons will be absorbed preferentially by the tagged elements and will subsequently create a cascade release of lower energy electrons via the Auger process that are in turn absorbed and destroy the cancerous lesion in which the cancer-targeting agent is accumulated. While the suggestion of cascade Auger therapy is not new, the required compact, high flux, monoenergetic X-ray sources needed for practical implementation of this idea have not heretofore existed.

The collaboration with LLNL will be carried out with a reciprocal LDRD project[12] of LLNL corresponding to the present proposal, while LLNL has already multibillion dollar

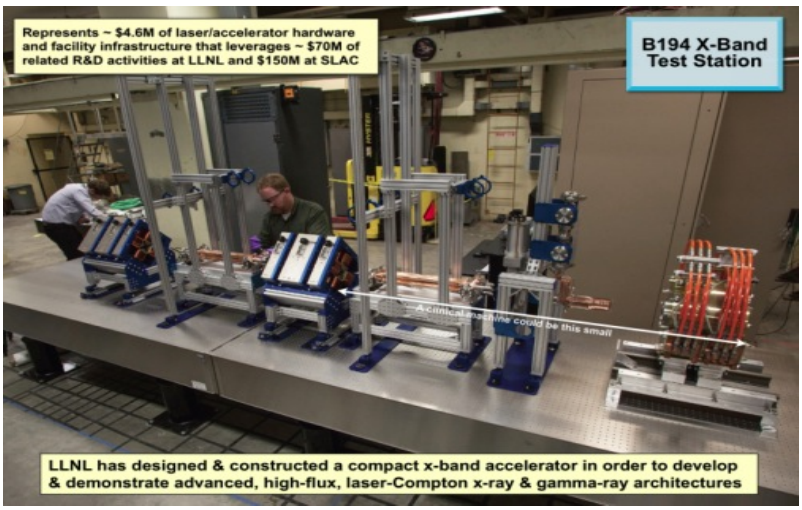

Figure 3. The LLNL laser-Compton test station is designed to test advanced concepts for high-flux x-ray generation and provide a capability for development of mono-energetic X-ray applications

investment on its laser facilities. The core part of the LLNL B194 X-band test station is shown in Fig 3. The laser engineering will be conducted in collaboration with the photonics companies of Southern California, such as Hamamatsu Photonics, Newport Optics, etc.

II. Research Projects

In this part of the grant, we first describe about the novel photon source in **(a)** and the Theranostic approach that we will pursue using this light source in **(b).** We describe two primary projects under this proposal in the first two years: (1) the K-edge contrast imaging described in **(c)**, (2) the radiotherapy using Auger electrons generated by the K-shell exciting X-rays in **(d).** In addition in the third year we will embark on other X-ray applications **(e)**: (3) phase contrast X-ray imaging (4) gated X-ray imaging[14], (5) the nuclear resonant fluorescence technique[15]. We also apply our laser technology to the following projects ultrafast laser surgery (glaucoma) in **(f)**, and laser-driven beam therapy of cancer in **(g).**

(a) Laser Compton X-ray Sources

Shortly after its introduction to clinical practice in 1973, computed tomography was rapidly shown to greatly increase the specificity and sensitivity of image information content. Since the mid 1990s fast, multislice, helical scanning multidetector, or multislice, computed tomography has advanced to include screening applications. Examples include CT colonography, lung imaging for early detection of cancer, and coronary artery calcification. Yet the technology underlying X-ray source hasn't changed much in these years. Electrons are still accelerated through glass vacuum tubes and slammed into target material at the end to produce X-rays. These sources are bulky, fragile, and limit the development of new generation scanners with higher spatial and temporal resolution. More importantly, the broadband X-ray beam generated by the conventional source doesn't allow utilization of other mechanisms than straightforward attenuation-based imaging that is the critical factor that limits the sensitivity of this high-resolution imaging technique, Fig 4. Due to its low sensitivity, X-ray CT is unfortunately not considered as one of the molecular imaging modalities (such high as PET or SPECT) although it provides unprecedented high resolution. *The ultimate application is to pave the way for moving this powerful imaging modality towards molecular imaging from its current status of standard anatomic imaging modality. Indeed, the Laser Compton X-ray technology will be the critical element to achieve this aim by opening possibility of utilization of other contrast mechanisms and hence, drastically increase the sensitivity.*

The advantages of the new generation sources proposed in this application is their spectral narrowness, tunability and utility as a pulsed X-ray source. These distinctive properties will allow utilization of this technique in several ways for enhancing X-ray imaging, Table 2.

UNIQUE PROPERTY	APPLICATION	ADVANTAGE				TIME-FRAME
		DOSE REDUCTION	HIGHER RESOLUTION	ENHANCED CONTRAST	REDUCED IMAGING TIME	
Narrow-band X-ray Beam	General Imaging	√				**Immediate**
Tunability	K-Edge Imaging	√	√	√		**Immediate**
	Radiotherapy	√	√			**Near-future**
Coherent X-rays	Phase Contrast Imaging	√	√	√		**Immediate**
Gating	General Imaging	√				**Near-future**
Pulsing	Time of Flight Imaging	√	√	√		**Near-future**
Narrow-band Spectrum	Nuclear Resonance Fluorescence (NRF)	√	√	√		**Near-future**

No Mechanical Motion	General Imaging				√	**Long-term**

TABLE 2. The advantages of this new X-ray source and its impact in the short- and long-term. In this application we will mainly focus on two that are highlighted with yellow.

(b) Theranostic Medicine Using Laser Compton X-ray Sources

In this application, we will mainly focus on two applications, K-Edge Imaging and radiotherapy using Auger electrons generated by the K-shell exciting X-rays (highlighted with yellow in the Table 2). The X-ray pulse with a specific energy that matches the K-shell level of an appropriate element is capable of producing a cascade of Auger electrons, which induce a local dose that can be used for therapy. Meanwhile, we will work on synthesis of disease, targeting high atomic weight elements such as gadolinum, iodine, platinum and gold. Note that gadolinum and iodine are the commonly used clinical contrast agents. Meanwhile, gold nanoparticles appear to be a promising contrast material in CT due to the high atomic number and tissue compatibility. These smart probes will allow for this theranostic approach, which integrates diagnostic imaging capability and therapeutic intervention. Laser based X-ray source described in this application will indeed be the key element for the proposed applications.

(c) K-Edge Imaging

The conventional X-ray sources are producing polychromatic bremsstrahlung x rays with a wide spectrum. Generating monochromatic or narrow-band X-rays instead, this new laser based X-ray source will limit the radiation exposure to just the useful X-ray photons, and also make the image contrast information more quantitative by eliminating beam hardening. In many circumstances this will reduce X-ray exposure. For example simulation studies demonstrated 10%-40% reduction in the chest and abdomen area when monochromatic beam is utilized[16]. Besides providing a narrow-band X-ray beam, the major advantage of the this new technology is its ability to tune the energy of the beam by either varying the energy of the electrons or the wavelength of the laser light. Conventional X-ray systems or X-ray computed tomography (CT) systems, equipped with currently available broad-band X-ray sources has to use energy-selective detectors for imaging of the distribution of elements with a high atomic number Z in the human body using Xray attenuation measurements. The focus of this approach is detection of element-specific, K-edge discontinuities of the photoelectric cross-section. Specifically, the target is imaging the local density of a gadolinium or iodine based contrast agents, in the framework of generalized dual-energy measurements - *one below and one above the K-edge absorption level.* The advantage of this approach is the higher sensitivity it provides due to the subtraction of these two measurements (K-edge subtraction imaging). Although extensive efforts have been spent in the last decade, it is still challenging to produce detectors that have high energy resolution and capable for high flux applications.

Laser-Compton X-ray Sources on the other hand can produce a narrow band X-ray beam and most importantly allow for tuning of the energy, Fig 4. Hence, instead of using a broadband conventional source and a special detector that can differentiate energy levels, this tunable source can be used with standard detectors to achieve K-edge subtraction imaging, Fig 5.

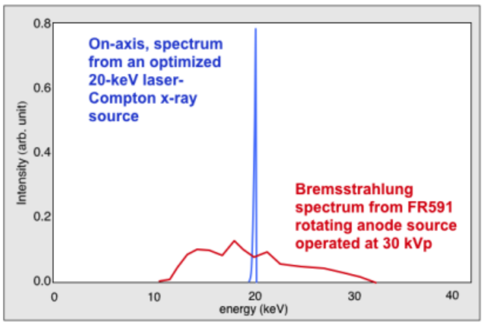

Figure 4. Red line shows the spectra of the FR591 rotating anode X-ray tube at 30kVp and blue line is the "***narrow spectrum***" of the Compton X-ray source at 20keV.

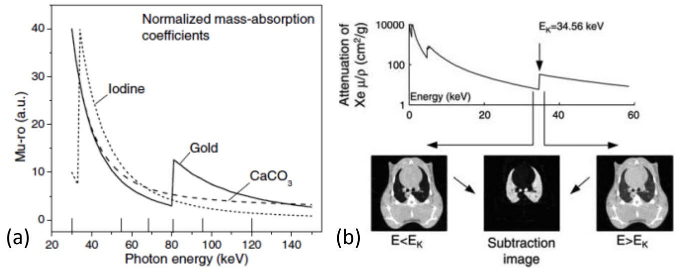

Figure 5. :(a) Normalized mass attenuation coefficients of three contrast materials. Acquiring images at energies below and above K-edge would allow quantitative imaging of these contrast agents with high sensitivity b) In ***K-edge subtraction imaging (KES),*** two simultaneous CT images are acquired using two x-ray beams at two different energies above and below the K-edge of xenon. Absolute quantity of the contrast agent is determined directly on any given point of a lung CT image after subtracting these two images on a logarithmic scale. (Bayat et al. 2006).

The current bottleneck for increasing the sensitivity of X-ray imaging is the performance of the energy selective detectors. Their energy resolution is far from perfect and on top, these detectors cannot properly handle high flux rates used in clinical imaging. With laser-based tunable X-ray sources, standard sensitive detectors can be used and the sensitivity of X-ray imaging can be increased since energy selective detectors are not required. In addition, laser-Compton X-ray sources produce pulses of X-rays from micron scale interaction regions and can enable new modalities of reduced-dose and high resolution imaging, phase contrast imaging, time-gated imaging, feedback imaging, etc.

To demonstrate this, we will perform phantom studies at LLNL. The CT phantoms will be fabricated from an acrylic cylinder with 14 cm diameter. The phantom will include several holes of with varying diameter (0.5 cm - 3 cm). The holes will be filled with different contrast materials such as gadolinum, iodine, platinum and gold with different concentration. Two different imaging configuration, pencil- and fan-beam, will be evaluated for K-edge subtraction imaging. Computer controlled rotation and translation stages will be utilized in the set-up. These proof-of-concept experiments will not only demonstrate the power of the laser-based X-ray sources but also allow the students to be trained in this technology as well as, X-ray imaging hardware, software and experimental design. Successful completion of this work will lay the foundation for follow-on, externally funded studies of additional imaging and therapy modalities enabled by laser-Compton X-ray sources.

(d) Radiotherapy Using Auger Process

(i) Targeted Contrast Agents:

Compared to conventional imaging modalities that predominantly offer anatomical pictures, molecular imaging interrogate cellular and molecular function and measure chemical and biological processes in the body. The contrast agents mentioned in the first specific aims are in general nonspecific agents. However, the very same agents can be modified to target disease related specific pathways and processes. Combined with the K-edge subtraction imaging that can be efficiently performed using laser-based X-ray sources as described in Aim 1, these targeted contrast agents will allow transformation of X-ray CT from anatomic to molecular imaging modality. Dr. Jered Haun's lab (one of the co-investigators) specializes in the synthesis of contrast agents for molecular detection and imaging applications. Specifically, his team synthesizes inorganic nanocrystals composed of iron oxide, semiconductor quantum dots, and gold. They also produce nanocarriers with silica, polymer, and lipid-based matrices. For this study, his team will contribute by producing nanoparticle contrast agents that contain gold, gadolinium, and iodine for molecular imaging of diseased tissue.

(ii) Theranostic Medicine using X-ray:

These targeted contrast agents can also be used for therapy once their accumulation at the disease site is confirmed with imaging. For this purpose, the tunability of this narrow spectrum laser-based X-ray source will be critical. The X-ray pulse with a specific energy that matches the K-shell level of the contrast agent is capable of producing a cascade of Auger electrons. These electrons will deposit their energy in a very short distance destroy the disease tissue. Since the agents would be targeting the diseased tissue the therapy will be very specific and local. Again the key element for this theranostic application would be the compact, high flux, mono-energetic tunable X-ray source. To show the feasibility of this idea, we will again use phantoms with holes that are filled with these contrast agents. Monte Carlo simulations will be used to determine the optimum parameters and estimate the deposited energy via Auger electrons. During the experiment, thermoluminescent dosimeters (TLDs) will be implanted around these inclusions to measure the deposited dose and compare with the simulations. These experiments and simulations performed prior to the experiments will provide an ideal platform to the students in the program. The preliminary data obtained during this study will be used to seek additional extramural funding to expand the program, mainly to build such a laser-based X-ray source at UCI, demonstrate the power of this theranostic approach using molecular probes with in vivo small animal studies and translate this exciting technology to the clinical arena in the future.

(e) Other Uses of the Laser-Compton X-ray Sources

Once the compact tunable narrow-band X-ray source is realized, it can also be used to enhance the contrast in different ways. Since the beam will be coherent, phase contrast X-ray imaging can be utilized. For example, in breast tissue contribution of the X-ray refraction to the complex index of refraction is 10000 times higher than the contribution due attenuation at 60 keV[17] Hence, phase contrast imaging will be much more sensitive compared to the conventional absorption based imaging. Since the proposed source in this application can be pulsed unlike the conventional sources that provides continuous output, direct measurement of the spatial distribution of the transit times of individual x-ray photons will be possible albeit the development of fast detectors with temporal resolution in the attosecond ranges that is expected to be achieved in a decade[18].

Prospective “gated” image acquisition, used in the case of the predictable cyclic motion such as occurs in the heart, can also reduce radiation exposure. This method involves acquiring incremental sets of partial-scan data only during a fixed phase of that cyclic motion progressively over many sequential heart cycles during one breath-hold. Total radiation exposure/scan sequence can thereby be reduced fourfold relative to retrospectively gated tomographic reconstruction, in which the x-ray exposure is continuous during the entire breath-hold duration of the scan. Another intriguing application of this technology can be Nuclear Resonance Fluorescence (NRF), using highly energetic monchromatic beam to cause nuclear states in the contrast elements to fluoresce. The detection of the emitted fluorescence X-rays will allow detection of these agents with high sensitivity. Finally, we envision to have smaller units of laser based electron accelerators (~several inches long) in the far future.

These very compact electron accelerators can be used to replace the large electron acceleration unit of this laser-based X-ray source. If this happens, there will be a breakthrough in X-ray imaging, since CT scanners with no mechanical motion can be produced by just illuminating these units sequentially using a powerful laser light. That will allow acceleration of data imaging to unprecedented rates, which will break the barriers of conventional X-ray CT imaging in a way that high resolution cardiac imaging will be finally possible. At this point, collaboration with companies such as Siemens, Philips, and others will be inevitable since such a source will open a new era in X-ray imaging.

(f) High Average Power Femtosecond Laser for Glaucoma Treatment

Based on the spectacular success of the LASIK[12] on the cataract treatment with the CPA laser[19] technology, we further foresee a new application of ultrafast lasers to glaucoma treatment. Femtosecond laser pulses with wavelengths tuned to the near-infrared range possess decreased scattering in translucent tissue. This allows simple beam delivery geometry through the translucent conjunctiva and sclera in order to create partial thickness sub-surface channels inside the semi-transparent sclera. These channels increase the outflow rate of the aqueous humor, therefore decrease the intraocular pressure (IOP). Significant reduction of the IOP in human cadaver eyes and in live rabbit eyes has been demonstrated indicating the potential of the method for the treatment of glaucoma.

With the currently available laser technology, however, the treatment time required to achieve the desired IOP reduction is 1 to 2 hours. Thus, the increase of the average power of the femtosecond laser is required to achieve practical treatment times of few minutes. Therefore, the high rep rated femtosecond laser technology[20] that has been proposed by some of the team members has important potential application for the treatment of glaucoma.

(g) Heavy Ion Beams from Laser Driven Technology

The interest of using heavy ion beams (e.g. protons, carbon ions) for the treatment of cancerous tumors in the United States has increased in recent years prompting many radiation oncology centers to acquire this technology. This interest on heavy ion beams is due primarily to the higher linear energy transfer (LET) at the tumor site denoted by their Bragg peak with virtually no dose deposition on healthy tissue beyond the tumor location. A higher LET directly correlates to a higher relative biologic effectiveness (RBE), which in principle translates to a higher rate of tumor cells killed[21,22]. The recent advance in the laser technology we have described now allows us to seriously consider the possible replacement of the costly and large conventional ion accelerators by that of laser based[23, 24].

The radiotherapeutic heavy ion beams with such lasers could be produced at a cost comparable to that of a state-of-the-art radiotherapy linear accelerator. A laser-driven compact beam could be used to produce a heavy ion beam in a treatment room space comparable to what is currently available in radiation oncology clinics reducing potential construction costs. In combination of the above described laser-driven enhanced X-ray diagnosis, we may have a prospect to have all-optical diagnosis-therapy integration here.

III. Research Collaborators

Toshiki Tajima, Norman Rostoker Chair Professor, Department of Physics and Astronomy, School of Physical Sciences, UCI

Gultekin Gulsen, Associate Professor, Department of Radiological Sciences, School of Medicine, School of Physical Sciences, School of Engineering, UCI

Christopher Barty, Chief Technology Officer, National Ignition Facility, LLNL

Gerard Mourou, Director and Chair Professor, International Center for Zetta- Exawatt Science and Technology, Ecole Polytechnique

Bruce Tromberg, Director and Professor of Beckman Laser Institute, School of Engineering, School of Medicine, UCI

Shaul Mukamel, Distinguished Professor, Department of Chemistry, UCI

Tibor Juhasz, Professor, Department of Ophthalmology, School of Medicine, School of Engineering, UCI

Dante Roa, Clinical Associate Professor, Department of Radiation Oncology, School of Medicine, UCI

Jered Haun, Assistant Professor, Biomedical Engineering, School of Engineering, UCI

Sabee Molloi, Professor, Department of Radiological Sciences, School of Medicine, School of Engineering, UCI

Xueqing Yan, Professor, Physics Department and Deputy Director of Institute of Heavy Ion Physics, Peking University

Xiaomei Zhang, Associate Professor, SIOM, visiting UCI under the Einstein Professorship Program of Prof. Tajima

Marcos Dantus, Professor Chemistry, Michigan State University