Potential ophthalmological uses of the FEL

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FEL-multiple wavelengths on demand

FIGURE 1. A superconducting radio-frequency linear accelerator drives Jefferson Lab’s kilowatt-scale infrared free-electron laser. After electrons are injected into and accelerated by the linear accelerator, they transit a wiggler magnet—yielding kW-scale light in an optical cavity.
Transfer of satellite imaging technology

FIGURE 1. An image cube has two spatial dimensions and one spectral dimension. The curves along the right show spectral reflectance values associated with individual pixels. The two curves at the bottom show the spectral radiance reaching the sensor and the corresponding spectral reflectance for vegetation.

Laser Focus World., May 2004, pg 76
Benefits and limitations of the eye as a research model

- Made to accommodate entry of light with many of its internal components visible and reasonably accessible
- Demonstrates a wide variety of responses to local and systemic pathologies
- Vital organ, susceptible to photodamage, ischemia, etc, with limited cellular regeneration
- Certain aspects of ocular functionality not easily tested in tissue culture/animal models
Please don’t look at the laser with your remaining eye
Free Electron Laser (FEL) Applications for Ophthalmology

- The T.R. Lee Center for Ocular Pharmacology is evaluating topical photodynamic (PDT) agents for treatment of pterygium, corneal neovascularization (CNV) and macular degeneration, as well as dermatological cancer models.
Free Electron Laser (FEL) Applications for Ophthalmology

- PDT agents permit ablation of blood vessels that compromise corneal clarity (pterygium, CNV) or retinal cell function (macular degeneration), as well as tumor cell disruption.
Benefits of topical preparations of photodynamic agents

• Reduced systemic toxicity
• Improved patient compliance/recovery
• Reduced amounts of drug required
Potential uses of FEL

| Macular degeneration, CNV, Pterygium, Cancer | Photodynamic therapy | Wide spectrum light source for testing PTD agents and regimens |
Current photodynamic agents have been designed around existing lasers

- Development of novel PDT agents would be accelerated by the availability of non-standard laser light from UV to IR which can be provided by the FEL and its ability to irradiate large numbers of animals for PDT screening
Test models

- Rabbit CNV
- Rat corneal transplant
- Primate/human corneal transplant
- In vitro, in vivo human
## Potential uses of FEL

<table>
<thead>
<tr>
<th></th>
<th>Detection</th>
<th>TeraHz, N(IR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveal cancer</td>
<td>Detection</td>
<td>TeraHz, N(IR)</td>
</tr>
<tr>
<td>Corneal transplant</td>
<td>Detection of rejection</td>
<td>TeraHz, N(IR)</td>
</tr>
</tbody>
</table>
Uveal melanoma
Hyperspectral scan of chicken tumor
TeraHz imaging of basal cell tumor
Confocal Microscope

- Uses spinning Nipkow disk to create a 5-7 um optical section
- Patient’s eye is anesthetized and applanated
- Video data recorded on VCR or digital files (tif, jpeg, etc)
TSCM - *in vivo* Tandem Scanning Confocal Microscopy

Furrer et al, J Ocular Pharm & Therapeutics, 1997; 13: 561
Cornea Transplant Rejection

Normal Rat Corneal Stroma

3 Day Rat Corneal Transplant-Stroma
Uveitis

Normal Rabbit Endothelium

Uveitis-Rabbit Endothelium
AC Fibrin & Leukocytes
ICE Syndrome: Confocal

Thickened corneal endothelial cells impair vision in glaucoma patients
Free Electron Laser (FEL) Applications for Ophthalmology

• The T.R. Lee Center has also developed a novel group of free radical scavengers that are known radioprotectants.

• These agents have a low molecular weight methoxypolyethylene glycol (MPEG) backbone that allows entry of the compounds into cells.
Free Electron Laser (FEL) Applications for Ophthalmology

• These agents can be formulated with different side groups, allowing them to chelate heavy metals responsible for free radical generation, as well as present reducing groups to sustain the cell against ischemic damage. Cellular penetration can be enhanced by the formation of MPEG esters.

• These agents have therefore potential for treating the free radical component of such ocular conditions as glaucoma, cataracts and macular degeneration, as well as heart attack, stroke and Alzheimer’s.
MPEG-methoxypolyethylene glycol)
Creation of esters to permit ready entry of MPEG derivatives into cells

MPDTE $n=7$, $MW \text{ ca.} 814 \ C_{35}H_{66}N_{4}O_{17}$

Methoxypolyethylene glycol $MW \ 350$ amide of diethylenetriaminepentaacetic acid, methyl ester
Some MPEG based chelators
MPEG attributes

• Ability to concentrate agent around cellular DNA
• Selectively protects against radiation damage to normal cells
• Reduces potential sources of free radicals, as well as detoxifying endogenous free radicals
Aqueous humor flow

CB ciliary body
R1 trab/Schlemm’s
R2 Uveoscleral
R3 Sclera
Pv IOP, episcleral vein
Glaucoma and IOP

Pressure elevations generally undetectable to patients
Glaucoma Test models

• Rabbit
• Rat episcleral vein ligation
• In vitro, in vivo human
Dose Response of MPDTE

<table>
<thead>
<tr>
<th>Time (Min.)</th>
<th>Change in IOP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>-8</td>
</tr>
<tr>
<td>T30</td>
<td>-6</td>
</tr>
<tr>
<td>T60</td>
<td>-4</td>
</tr>
<tr>
<td>T90</td>
<td>-2</td>
</tr>
<tr>
<td>T120</td>
<td>0</td>
</tr>
<tr>
<td>T180</td>
<td>2</td>
</tr>
<tr>
<td>T240</td>
<td>4</td>
</tr>
</tbody>
</table>

- 3.0 mM MPDTE
- 8.7 mM MPDTE
- 1.0 mM MPDTE
- 3.0 mM MPDTE
- 1.0 mM MPDTE
- 0.3 mM MPDTE
Effect of different MPEG compounds at 30 mM
Amifostine, a clinical effective free radical scavenger does not lower IOP.
Electroretinogram basics

B wave = rods

A wave = cones
A Wave amplitude

Control
Week 0

Weeks after NMDA

Week 2

Arbitrary units

NMDA
NMDA + MPDTE
NMDA + MPSEDE
B Wave amplitude

Arbitrary units

Control
Week 0

Weeks after NMDA

Week 2

NMDA
NMDA + MPDTE
NMDA + MPSEDE
## Potential uses of FEL

<table>
<thead>
<tr>
<th>Glaucoma</th>
<th>TeraHz</th>
<th>TeraHz</th>
<th>N(IR)</th>
<th>UV-N(IR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt and valve function and integration into tissue</td>
<td>terrestrial</td>
<td></td>
<td></td>
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<tr>
<td>Structural alterations affecting aqueous humor flow</td>
<td>terrestrial</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Drug depots and long term drug release</td>
<td>terrestrial, N(IR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of retinal ganglionic cells, measurement of retinal pigments</td>
<td>terrestrial, N(IR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic changes, production of free radicals, ischemia</td>
<td>terrestrial, UV-N(IR)</td>
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</tbody>
</table>
TeraHz time domain spectroscopy
TeraHz detection of tooth decay
Cataract formation

- UV and cosmic radiation
- Drugs
- Trauma
- Diabetes, Down’s, Glaucoma, etc.
Current limitations of cataract detection and treatment

- Slit lamp detects frank cataract formation often years after precipitating events
- Surgical treatment used to replace lens
- Necessity to follow early events to monitor efficacy of interventions as well as to track the pathology of disease process
Cataract Test models

- Mouse X-ray, UV, chemical
- Rat X-ray, UV, chemical
- In vitro, in vivo human
Free Electron Laser (FEL) Applications for Ophthalmology

- The FEL can be used to generate ultraviolet radiation damage models to test the efficacy of MPEG agents to protect against cataract formation and UV skin damage.
Free Electron Laser (FEL) Applications for Ophthalmology

• The FEL can be used to develop (N)IR and terahertz radiation imaging technology which can be used to detect changes in the hydration of the lens that occur during cataract formation, as well as the presence of tumors in the skin and body, changes in retinal pigments that indicate retinal dysfunction and myloid plaques (Alzheimer’s disease).
## Potential uses of FEL

<table>
<thead>
<tr>
<th>Cataracts</th>
<th>Creation of animal models</th>
<th>UVA, UVB radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early detection of capsule and lens changes</td>
<td>TeraHz, N(IR)</td>
</tr>
<tr>
<td></td>
<td>Detection of IOL rejection</td>
<td>TeraHz, N(IR)</td>
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</tbody>
</table>
Ocular Hb oxygenation detection

Biophotonics Inter., May 2004
Measurement of Biochemical Parameters

Raman Spectroscopy

• Pharmacokinetic studies
• In vivo drug measurements and metabolite levels
• Localization of drugs – diffusion and compartmentalization
Raman Ocular Glucose detector

Blood-sugar levels are measured through the eye with a Raman spectrometer.
Confocal raman microscope

Figure 1 A confocal Raman microscope consists of a dual-output-port spectrometer integrated with a confocal microscope. A singlemode optical fiber provides point-source illumination and the core diameter of a multimode fiber provides the confocal pinhole in the focal plane.
Researchers used Raman spectroscopy to identify single microbial cells such as the ones pictured in the top right. A typical Raman spectrum for a single cell is shown at the bottom. Reprinted with permission from Analytical Chemistry.
Age related macular degeneration

• Major cause of vision loss
• Interventions include PDT, drugs, etc.
• Interventions have limited efficacy on this progressive disease
• Future interventions for retinal repair/replacement via stem cells, artificial retina
Dresen on retina of AMD patient
AMD, Diabetes, Dry eye test models

- Mouse
- Rat
- In vitro, in vivo human
Potential uses of FEL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular degeneration</td>
<td>Detection of dresen, retinal pigments, drug depot function</td>
<td>TeraHz, N(IR)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>Progressive corneal surface changes</td>
<td>TeraHz</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Detection of corneal and retinal changes</td>
<td>TeraHz, visible-N(IR)</td>
</tr>
</tbody>
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T.R. Lee Center team

- Patricia Williams, PhD Director
- Earl Crouch, MD Chairman Ophthalmology
- John Sheppard, MD, MMSc Clinical Director
- Frank Lattanzio, PhD Basic Science Director
The Beginning
Schematic of imaging spectrometer

FIGURE 2. Two designs for an imaging spectrometer are a pushbroom design (left) and a line-scanner design (right).
IR cell chemical scan

Figure 1. A chemical mix on a plate (visible image at top left) is represented by a characteristic cube where the front face is an infrared image at one wavelength, succeeding slices are images at increasing wavelengths, and on the right face is traced the absorbance intensity for various species at increasing wavelength.