Laser Bioscience Workshop:
Applications of Free Electron Lasers for Bioscience and Biomedicine

June 7-8, 2005
Newport News, VA

The Jefferson Lab Free Electron Laser Facility: Current and Future Capabilities for Bioscience

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The Jefferson Lab Free Electron Laser

developed by the

Laser Processing Consortium

managed by

Thomas Jefferson National Accelerator Facility
(Jefferson Laboratory)

Aerospace Corporation
Advanced Energy Systems
Dominion Power
Dupont
IBM
Northrop Grumman
PLD, Inc.
Siemens
3M

Office of Naval Research
Naval Research Laboratory
NASA Langley Research Center
Southeastern Universities Research Association
Optoelectronics Research Center, Southampton University
Fraunhofer Institutes
Air Force Research Laboratory
US Dept. of Energy
Virginia Center for Innovative Technology

Free Electron Lasers (FEL)

- A type of laser invented in 1977 that extracts laser light from a fast moving electron beam in a vacuum pipe- is freed of the limitations of conventional lasers
- The output wavelength (color) is tunable from the far infrared (THz) through the visible to the ultraviolet (<60nm)

- The power output can be made very large, because there is no waste heat to be removed from a solid, liquid or gaseous laser medium

- **At high power, the cost per unit of light delivered can be very attractive**
- **Producing a series of very short pulses (<ps), the FEL processing efficiency can be much higher than conventional lasers**

FELs : Setting the Context for Bioscience

- ~40 FELs exist worldwide for scientific applications

- Pioneering work has been done on the application of FELs for bioscience and biomedicine at the Stanford, Vanderbilt and Duke FEL Centers (managed by the AFOSR Medical FEL Program)

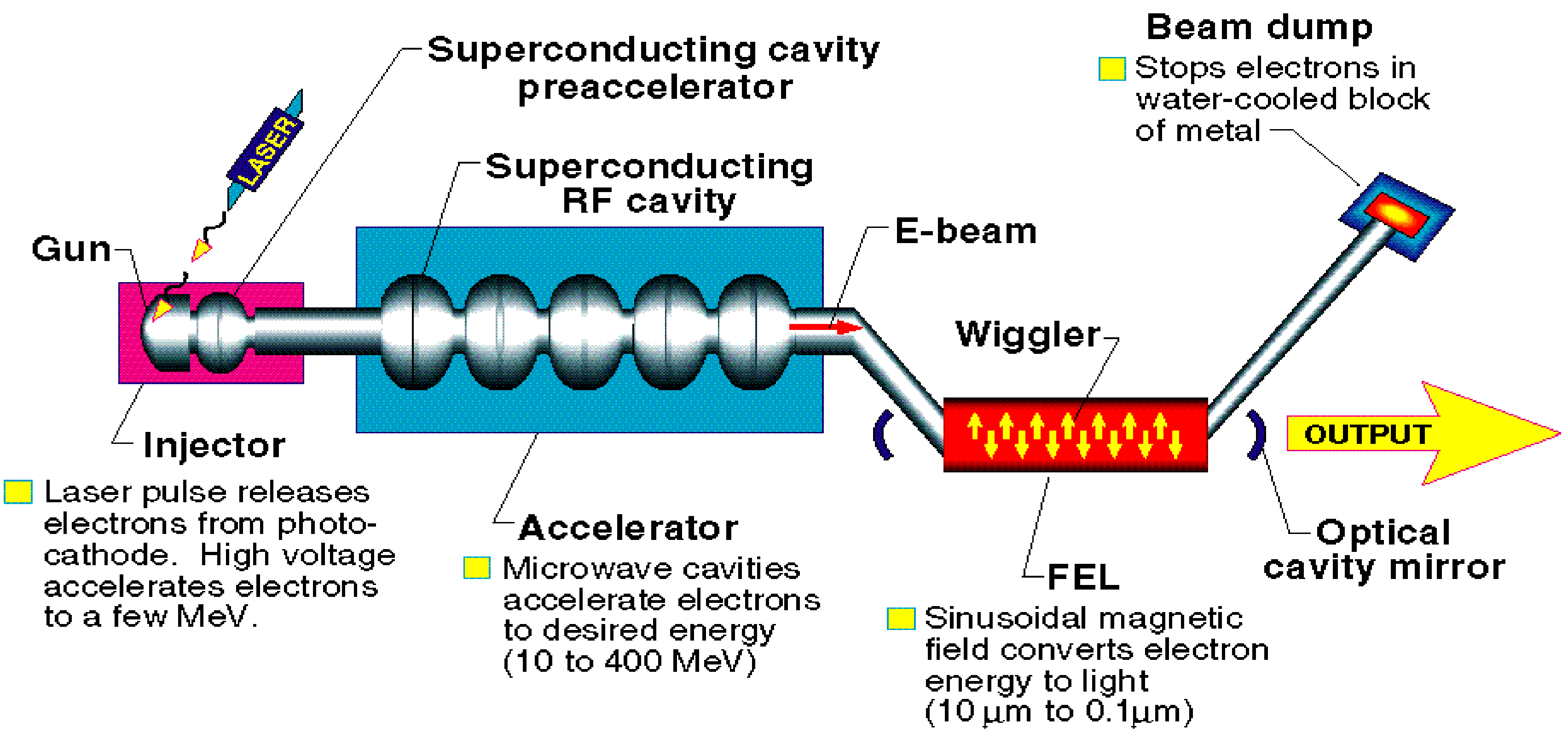
"The Council of the ASP recognizes the potential impact of high performance Free Electron Lasers (FELs) in fields of interest to our members, particularly photomedicine and environmental photobiology. Achieving these opportunities will require appropriate support facilities. The ASP Council therefore strongly encourages the development of facilities to support biological and medical research at existing and/or new FELs."

-Council of the American Society of Photobiology, Feb. 2005

FEL Applications to Photobiology and Photomedicine
- a partial list:

- Protein sorting, gene expression studies with laser-mass spectroscopy
- UV and near UV Photodamage to biological systems
  - Important for the "ozone" problem; sunscreen development
- Photodynamic Therapy (PDT) and other photo-therapies
  - Expansion of a promising and simple cancer therapy
- Ballistic Imaging in the Visible – IR
  - A non-ionizing (i.e., zero consequence) medical imaging, technique
- Infrared microscopy
  - An expanded microscopic technique which gives chemical identification

Components of a Free Electron Laser



Free Electron Laser Development at Jefferson Lab

- Designed, built and commissioned highest average power FEL (IR Demo) in 1996-98
  - achieved 2.1 kW at 3.1 microns (previous world record, 11 watts)
  - demonstrated power efficiency by lasing at 2.1 kW while recycling and recovering more than 75% of the input linac energy
  - Also produced world class powers in the FIR (THz), visible, UV and x-ray

- Established a versatile User Facility for the IR Demo FEL:
  - materials science and processing
  - photochemistry/photobiology
  - microfabrication
  - used by 30 research teams in 1999-2001

- IR Upgrade to 10 kW completed in July 2004: new world's record 10.6kW

- UV Upgrade (> 1 kW) coming in 2005

Superconducting Nb RF accelerator cavity array at Jefferson Lab

1.497 GHz

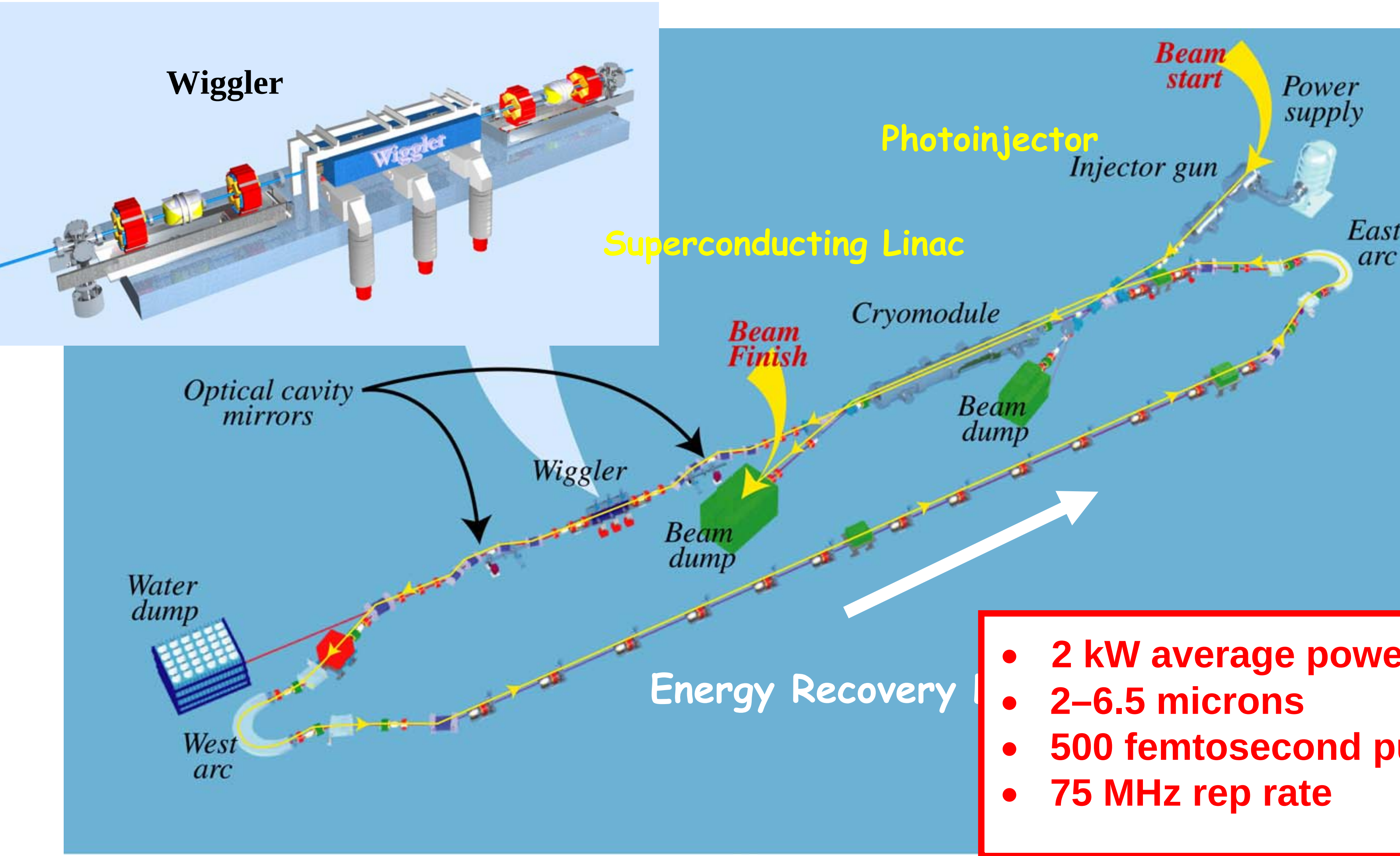
2.2 Kelvin operating temperature

Operates up to 12 MV/m

New designs show >20 MV/m

The JLab IR Demo Laser

the world's most powerful femtosecond laser
the world's most powerful tunable IR laser

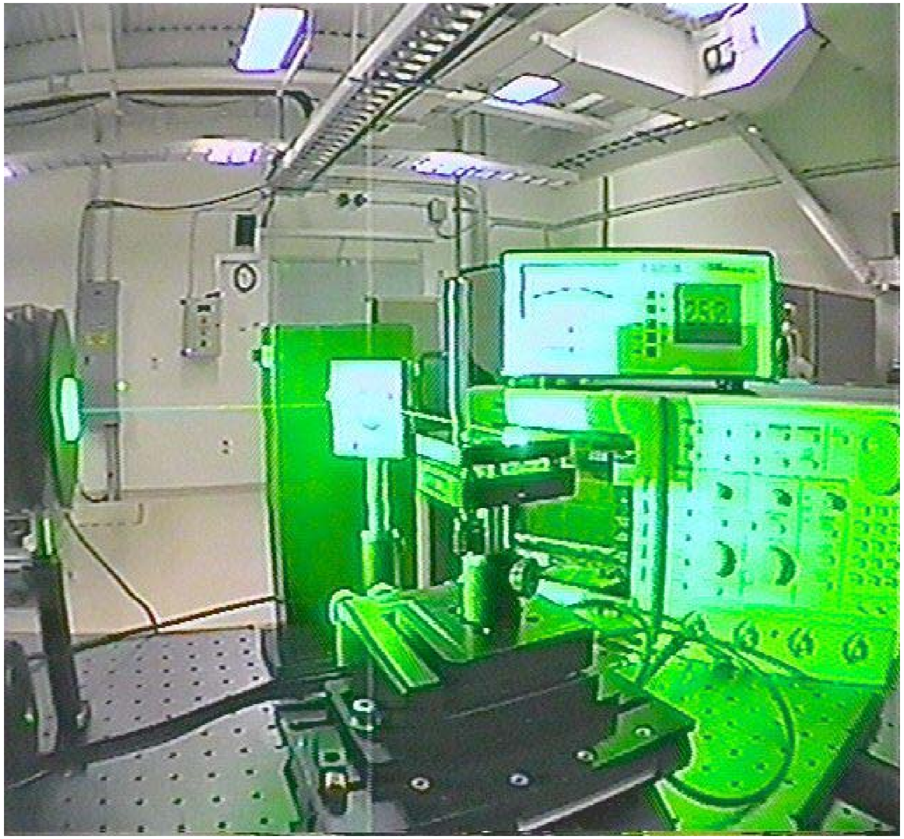


- **2 kW average power**
- **2–6.5 microns**
- **500 femtosecond pulses**
- **75 MHz rep rate**

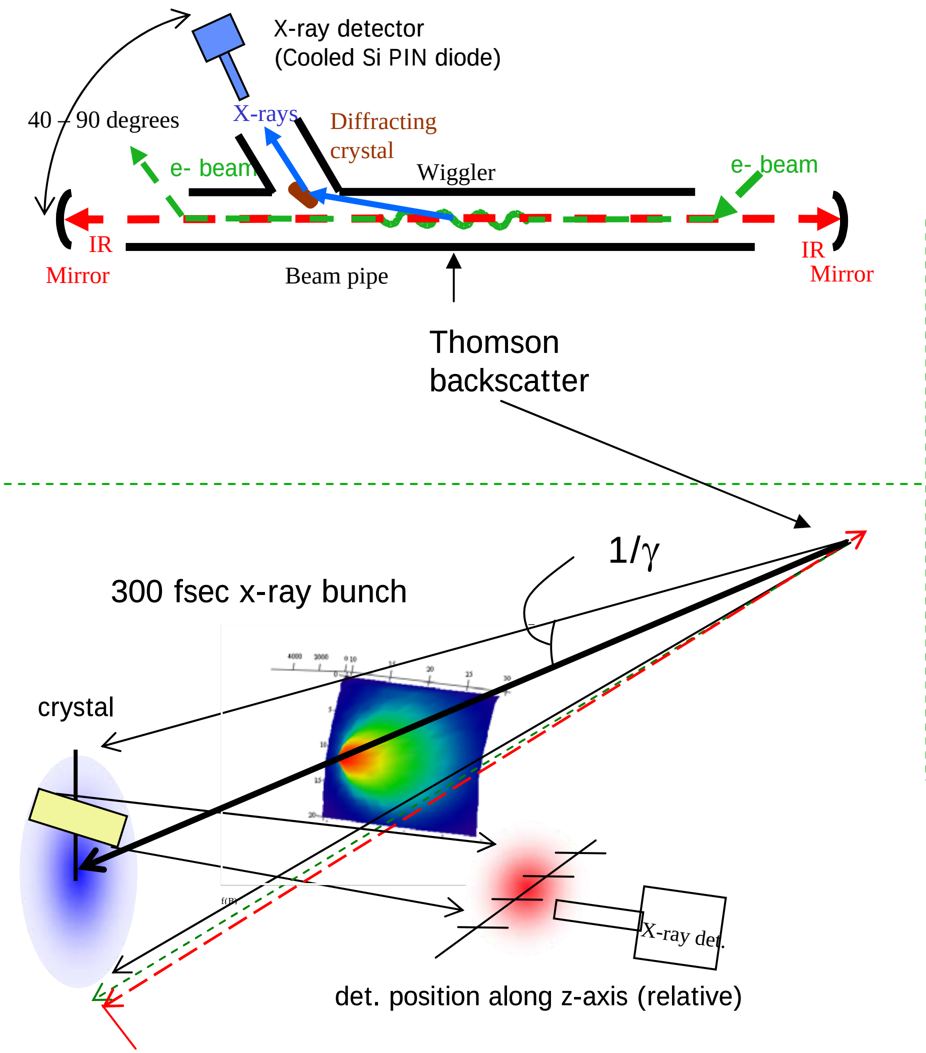
JLAB FEL Harmonic Generation

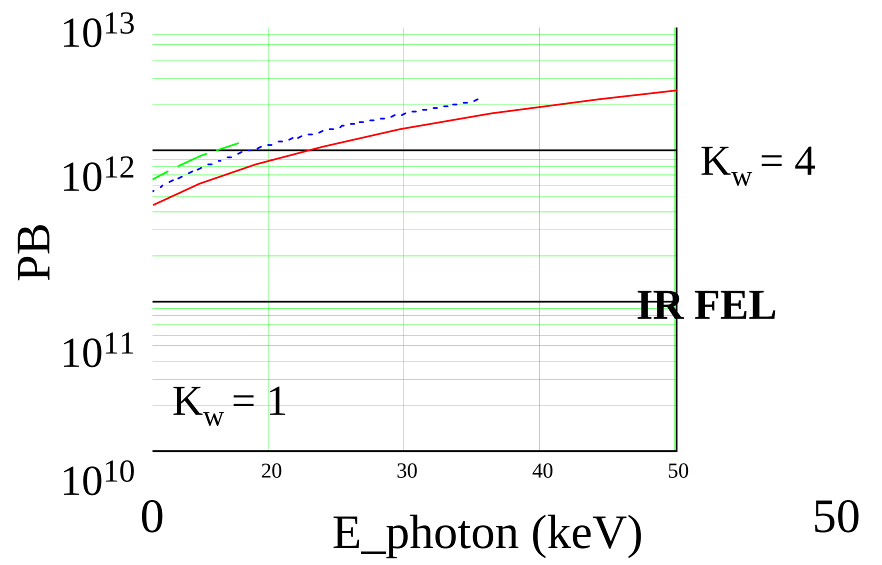
Wavelength	Conversion efficiency	CW Power (Watts average)
Fundamental 3.165 mm	1.6% (ebeam:light)	2100*
Lasing 3rd Harmonic 1.055 mm	0.7% (ebeam:light)	350*
2x 528 nm	40%	56*
3x 352 nm	9%	12*
4x 264 nm	8%	17 (pulsed)

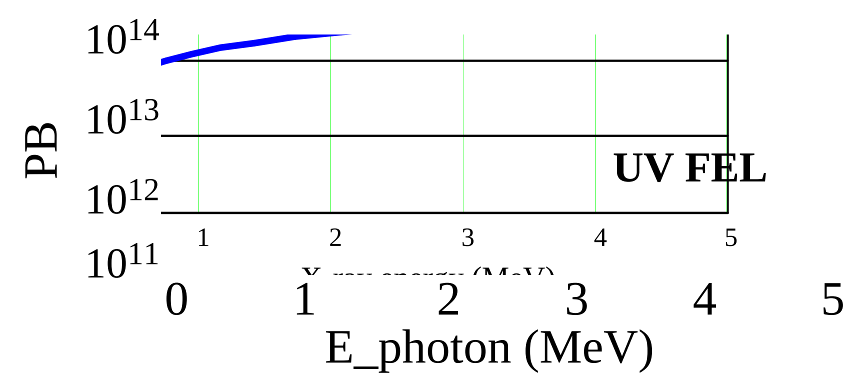
*World record for picosecond laser



X-rays from IR Demo & Upgrade

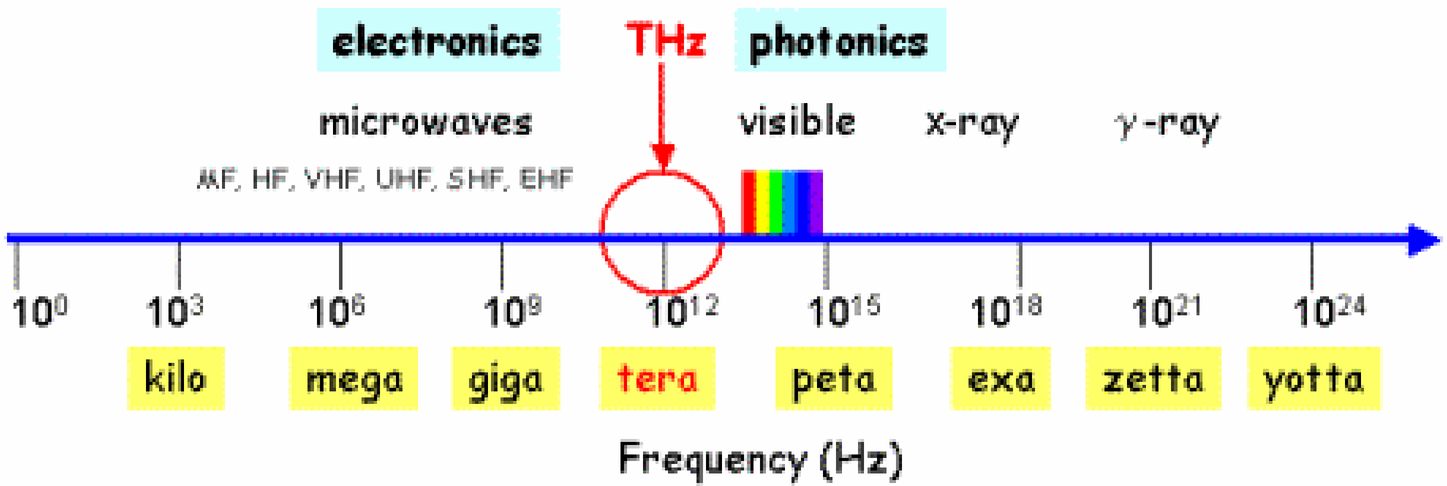






PB: Peak Brightness (ph/sec/mm^2/mrad^2/(0.1%BW))

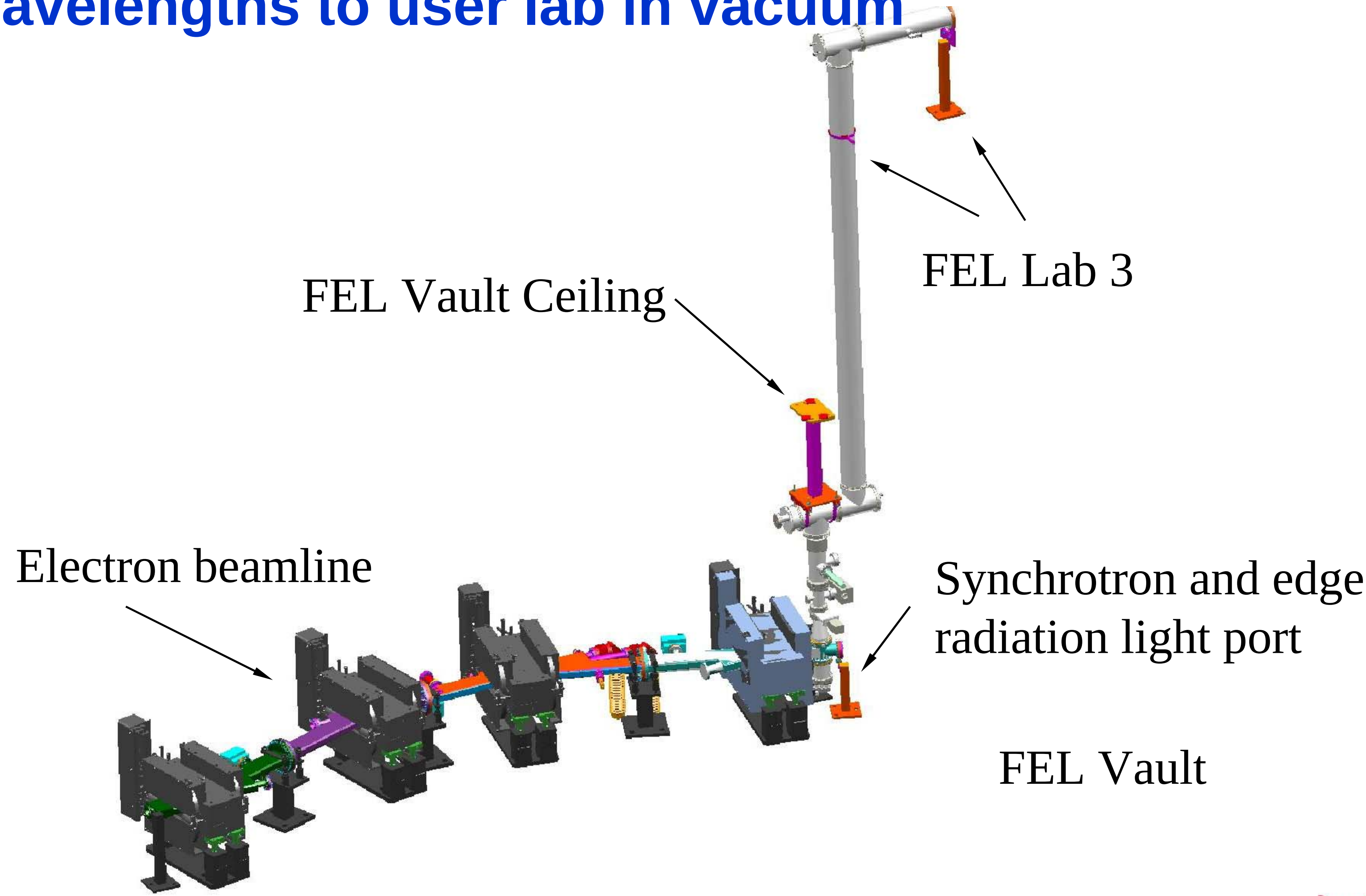
THz: a Frequency Range with Rich Science but Limited Technology



1 THz ~ 1 ps ~ 300 μm ~ 33 cm^{-1} ~ 4.1 meV ~ 47.6 °K

http://www.rpi.edu/~zhangxc

Terahertz beamline transports visible to 5 mm wavelengths to user lab in vacuum



JLab THz Beamline Users on Deck

Users with preliminary proposals, or who have indicated interest:

Tatiana Globus, UVa, spectroscopy of biological materials including DNA, polynucleotides and tissue, to establish dynamical processes and contrast mechanisms for imaging.

X.-C. Zhang, RPI, large area real-time imaging development using electro-optic detection methods and large imaging crystals.

G. Williams, JLab, and L. Carr, BNL, spectroscopy and scattering of particulate matter relevant to army program, initial experiments in June 2004 at Brookhaven.

A. Sievers, Cornell, non-linear dynamical studies of iron oxides, generation of localized modes. Development and testing of novel "shear" wavelength multiplexing interferometer.

Bob Jones, UVa, creation of Rydberg atoms and dynamical studies.

Martyn Chamberlin, Durham, UK, use of high power THz light to bleach water absorption in biological samples.

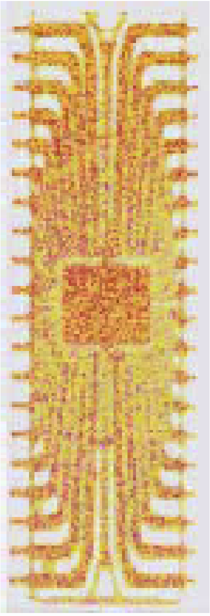
Dan Mittelman, Rice U., use of high power THz for imaging modality studies.

Bob Austin, Princeton, energy transport in biomolecules

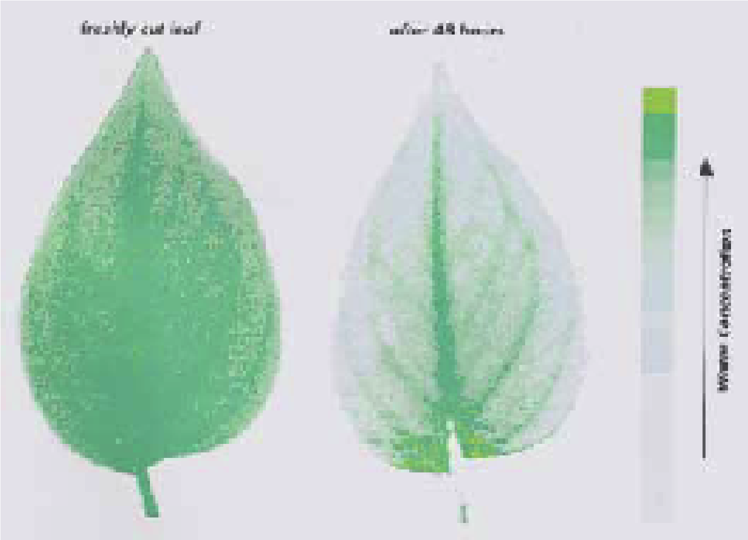
Opt. Lett. 20, 1716 (1995)

Imaging with terahertz waves

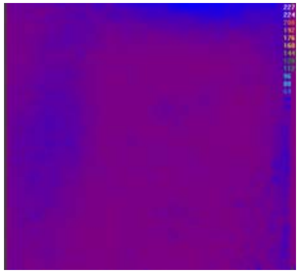
B. B. Hu and M. C. Nuss



THz image of an IC chip



THz images of a fresh leaf and of the same leaf after 48 hrs

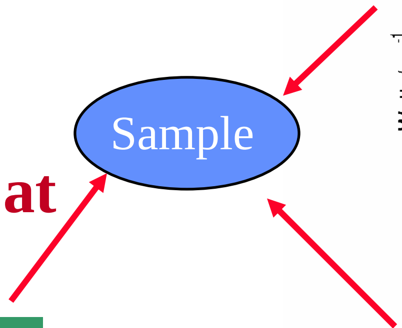


http://www.rpi.edu/~zhangxc

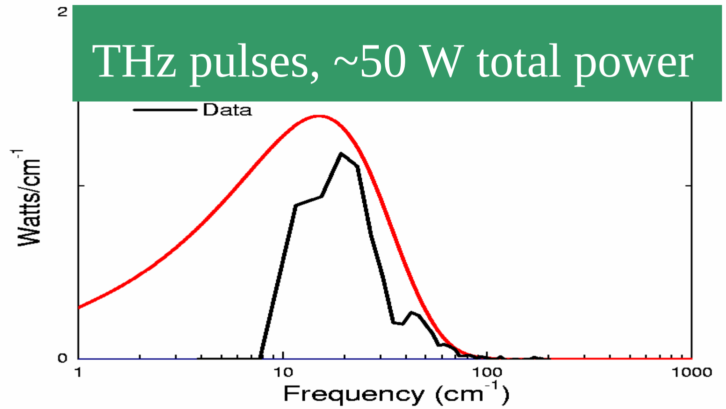
Simultaneous production of 3 μm, THz, and 10 keV X-ray femtosecond pulses

- **800 fsec pulses at 37.4 MHz**
- **Synchronized to <<psec levels (same beam!)**

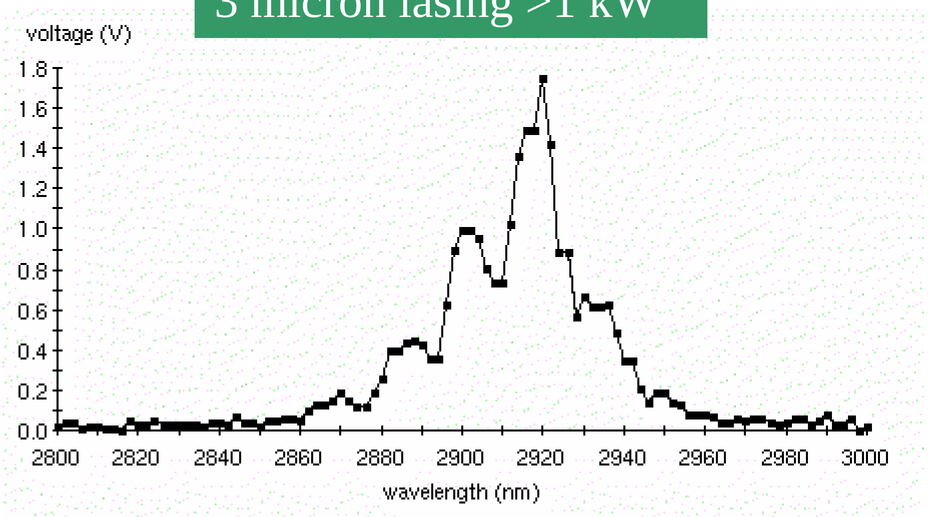
•All three wavelengths at world class fluxes



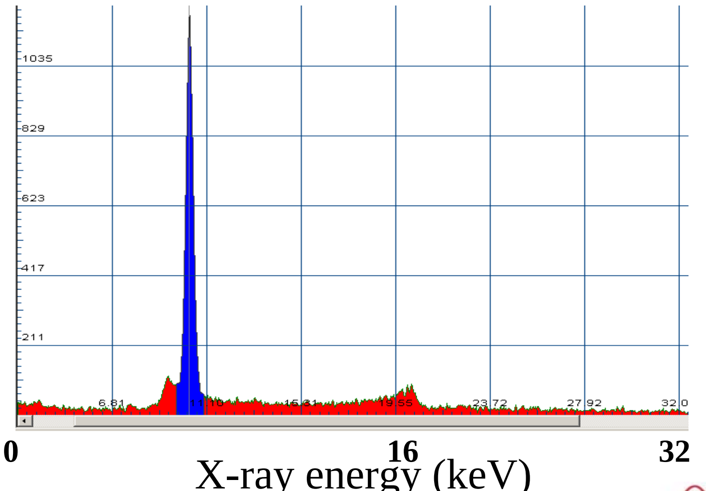
THz pulses, ~50 W total power



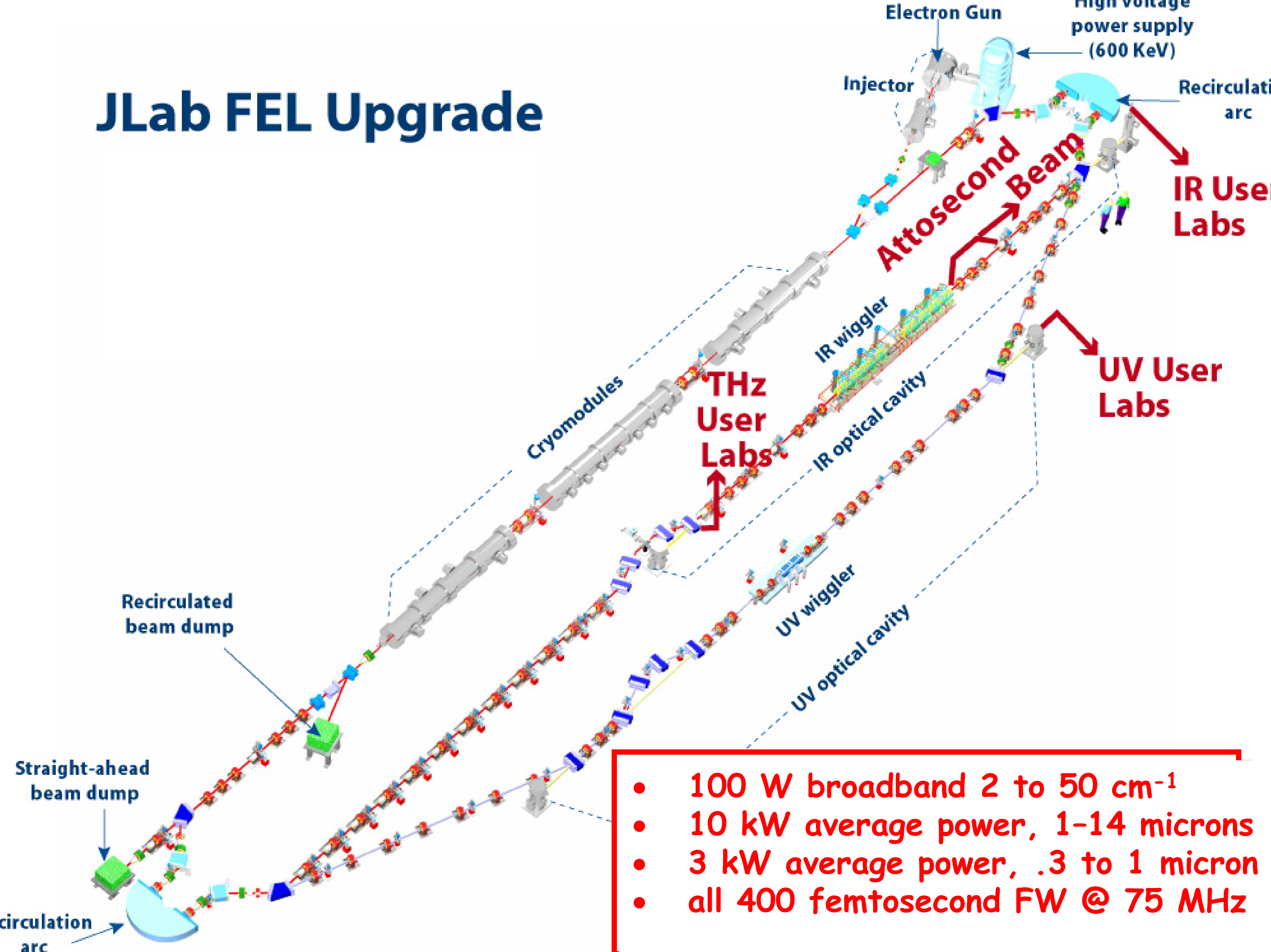
3 micron lasing >1 kW



10 keV X-ray > 10^5 ph/sec/0.1% BW

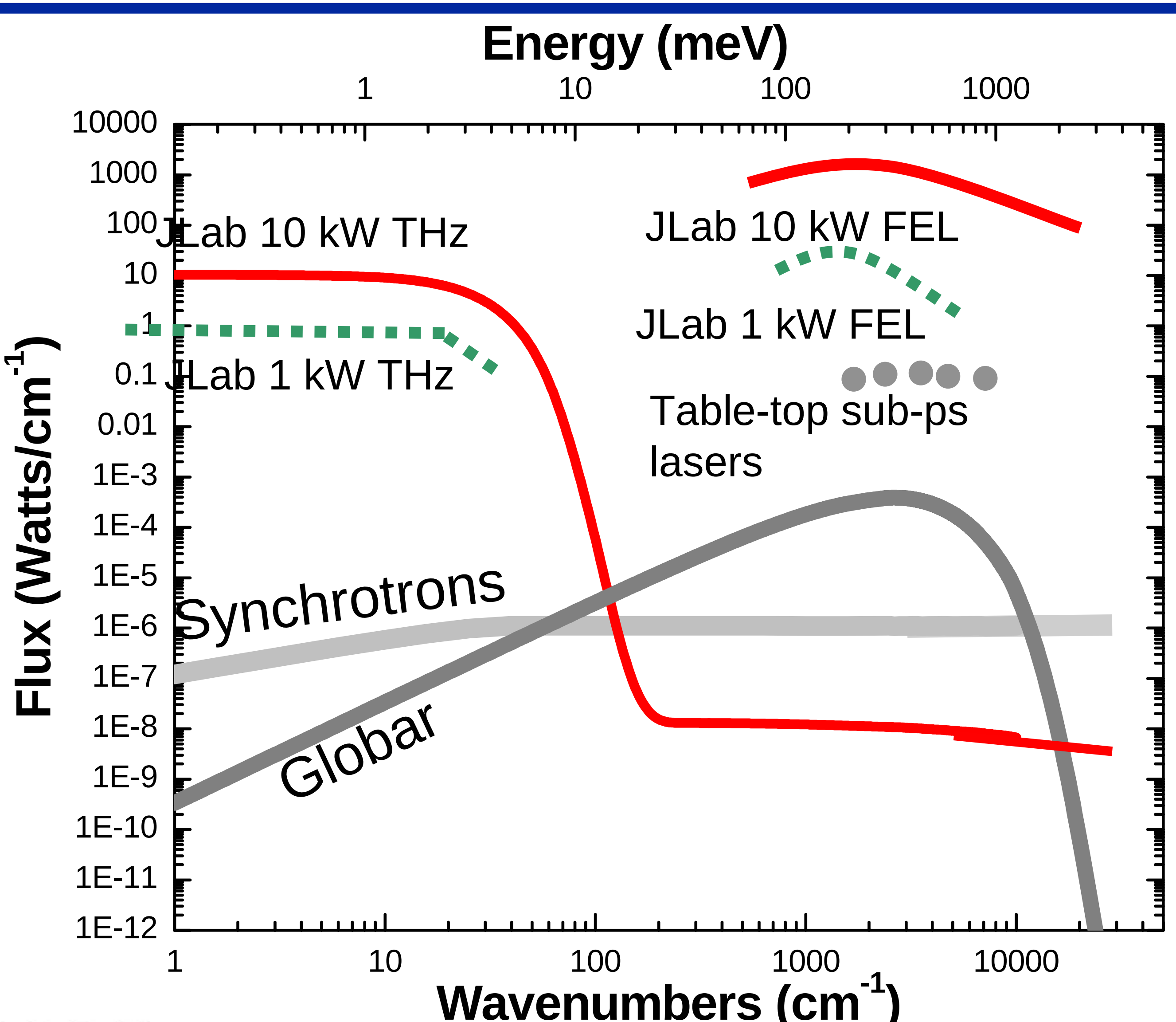


JLab FEL Upgrade



- 100 W broadband 2 to 50 cm^{-1}
- 10 kW average power, 1–14 microns
- 3 kW average power, .3 to 1 micron
- all 400 femtosecond FW @ 75 MHz

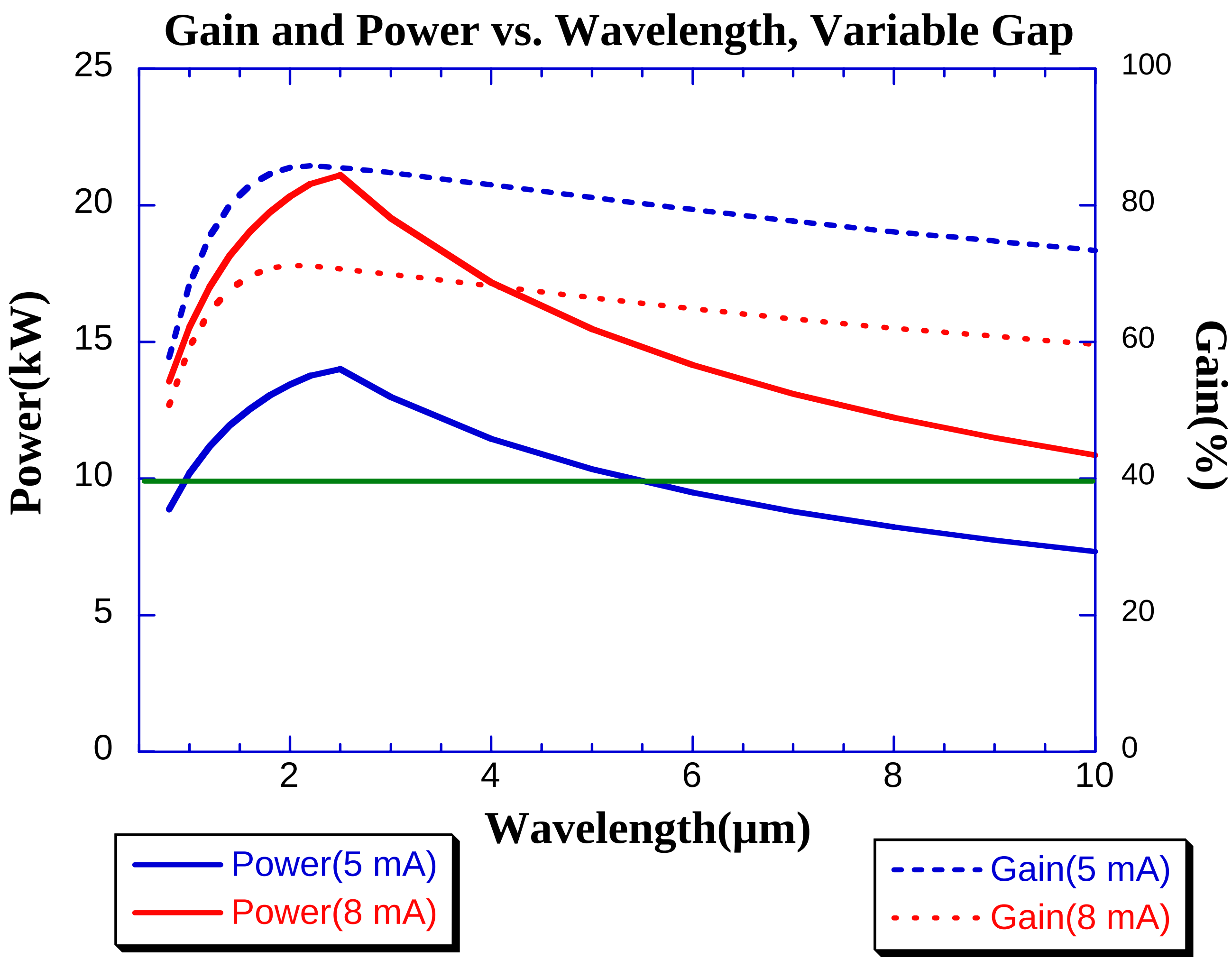
JLab FEL Power vs Conventional Sources



IR Upgrade Specifications

Average Power	> 10,000 W
Wavelength range	1 to 14 μm
Micropulse energy	> 100 μJ, in pulse train 50 μs to CW, arbitrary prf
Micropulse length	~0.1-2 ps FWHM (adjustable)
PRF	74.85 MHz ÷ 2x down to 4.68 MHz
Bandwidth	~ 0.2–3 % (always Fourier transform limited!)
Position/Angle jitter	< 100 um, 10 μrad
Polarization	linear, > 1000:1
Transverse mode	< 2x diffraction limit. Gaussian profile
Beam dia. at lab	2 - 6 cm, wavelength dependent

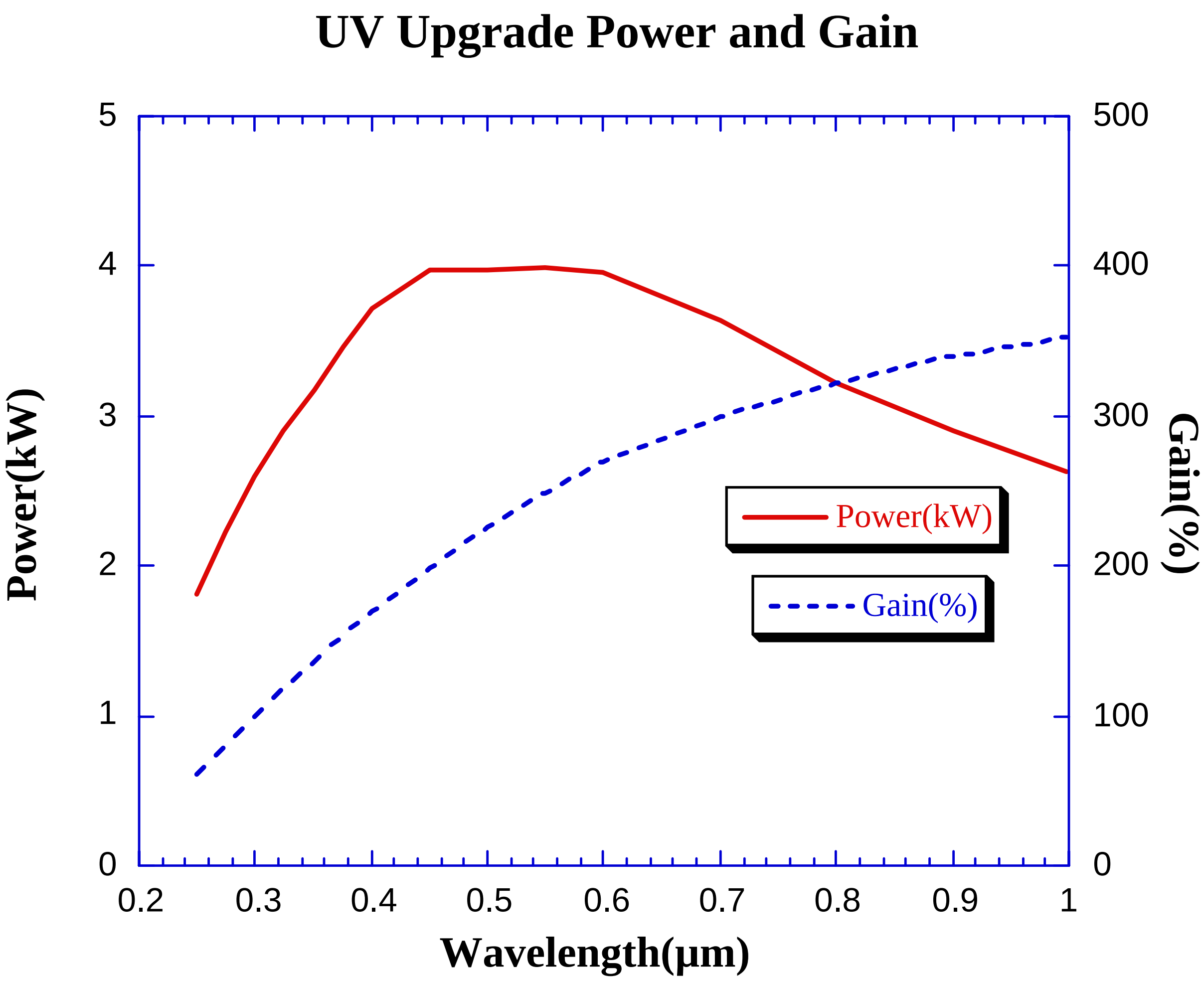
Performance with Variable Gap PM Wiggler



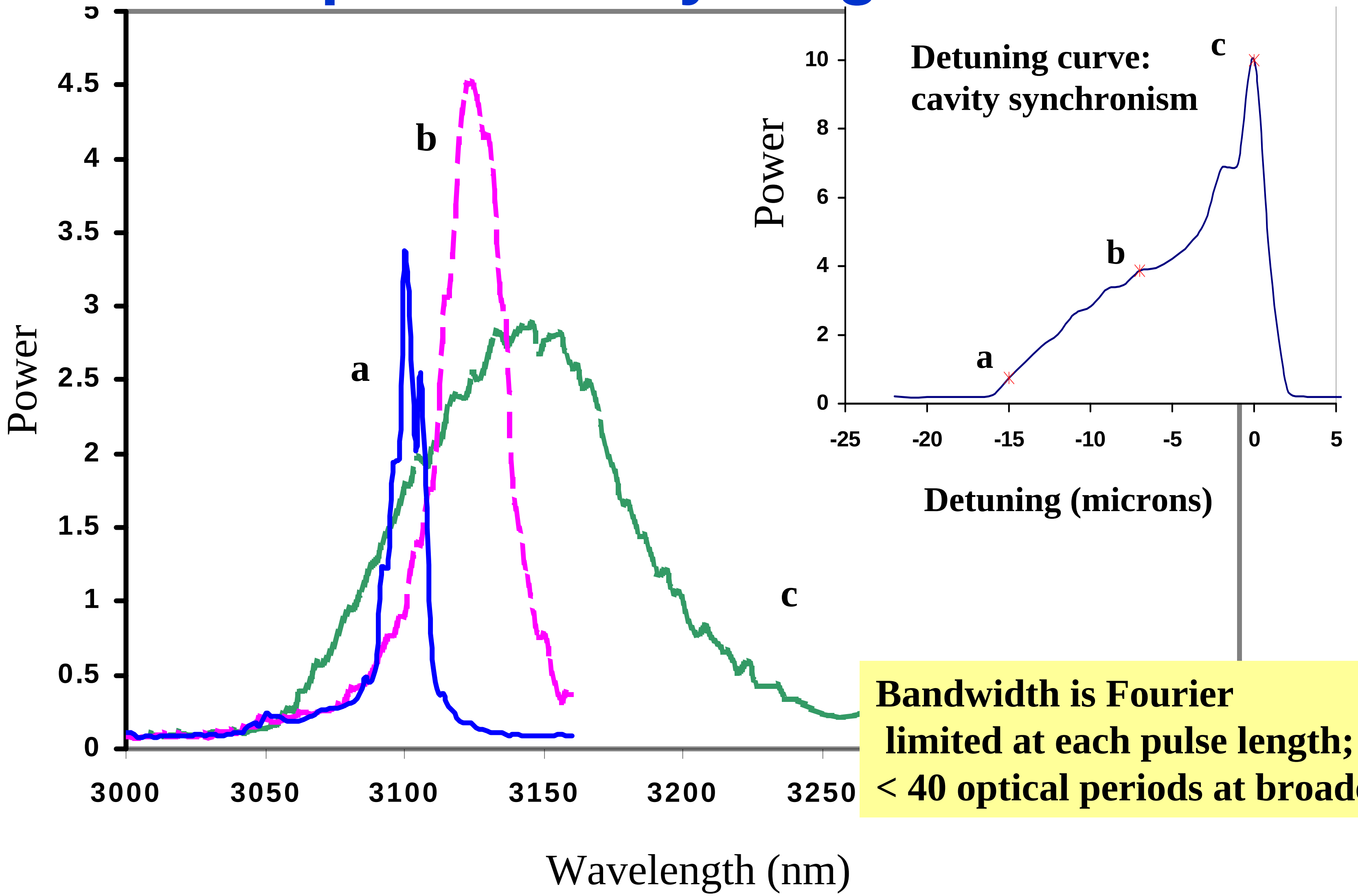
Minimum beam energy=80 MeV, Energy <160 MeV. Energy spread constant

UV Upgrade Performance: Installation next summer

- **Tunable pulse energy to saturate electronic transitions**
- **Drive non-linear field effects**
- **High rep rate for S/N: e.g., molecular beams, gas phase**



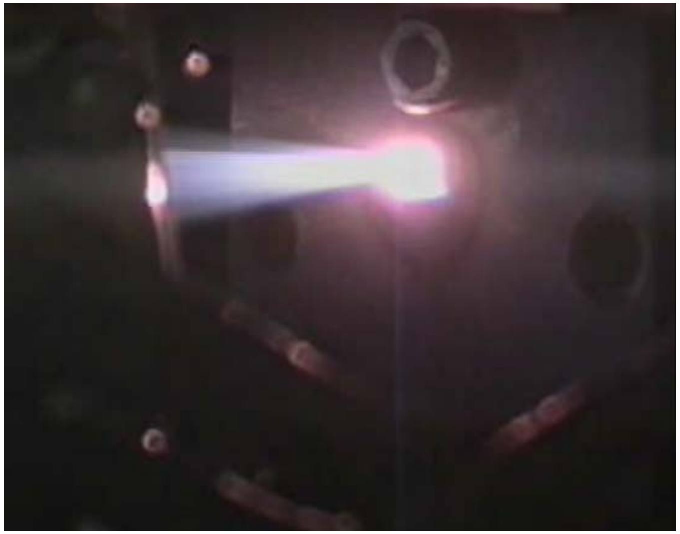
IR Demo measured bandwidth varies as a function of optical cavity length



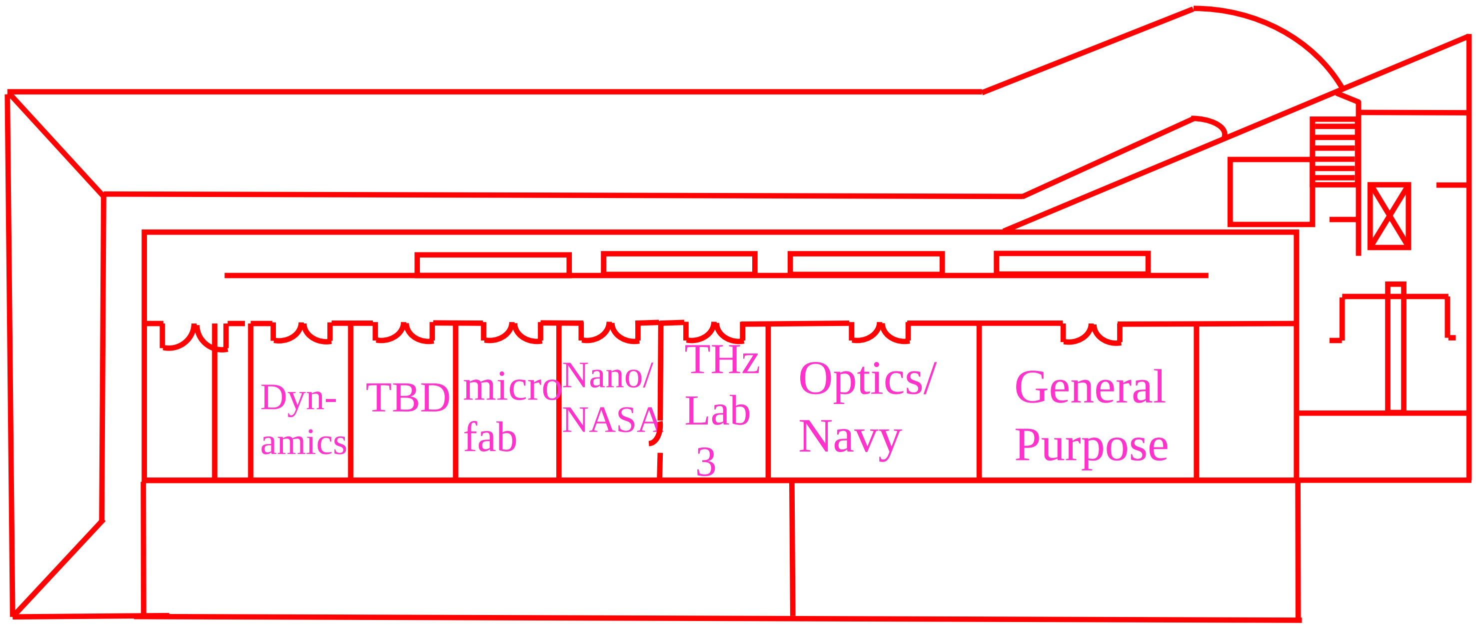
Bandwidth is Fourier limited at each pulse length; < 40 optical periods at broadest!

FEL User Facility at Jefferson Lab

- The FEL is housed in versatile user facility where scientists are developing unique applications of the FEL for basic science, industrial, biomedical and defense



JLab FEL User Lab Layout



Lasing Capability/User Lab Status – IR Upgrade

- We have several sets of high power mirrors capable of multi-kW but these are narrow band
  - 6 microns, 2.8 microns, 1 microns, (1.6 microns, (2.2 microns on order)
- We also have hole outcouplers and broadband mirrors for lasing from 1 to 10 microns at ~ 50 W output
- Instantaneous tuning is limited only by wiggler (K^2 goes from ~0.7 to 1.1

Status:

User Lab 1 Recommissioned in April (in use)

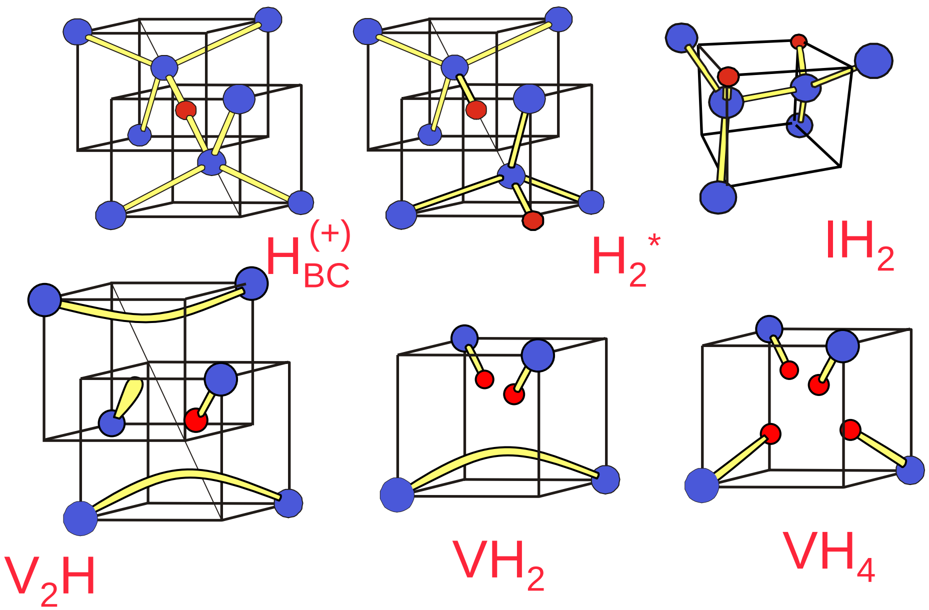
THz Lab (3a) next in line

Microfab Lab (4) this summer

Synopsis of FEL User Results: 2000-2001

- Spectroscopy
  - H-Si (Luepke, CWM)
  - Amide-I in myoglobin (Austin, Princeton)
- Ablation
  - Resonant PLD of polymers – (Kelley, CWM; Haglund, Vanderbilt)
  - Non-resonant, high quality magnetic/SC films – (Reilly, CWM; Shinn, JLab)
- Micro/nano-fabrication
  - C-nanotubes – (Holloway & Smith, CWM, NASA, PSU)
  - UV/visible micro structuring of glasses (Helvajian, Aerospace Corp.)
- Surface processing (Kelley)
  - Laser nitriding of metals (Schaff, Göttingen)
  - Laser amorphization of metals (Kessel, Dominion Power)

Science with the JLab FEL - H/Si



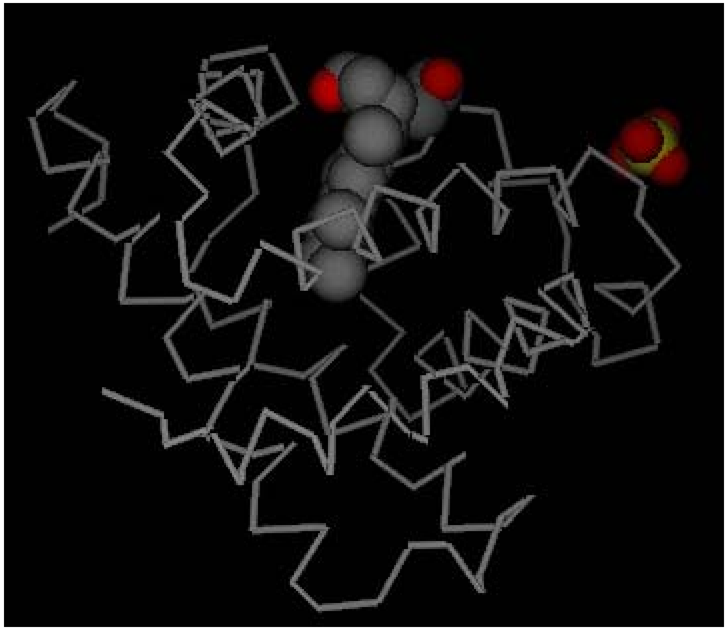
Luepke et al. CWM
Feldman et al. Vanderbilt

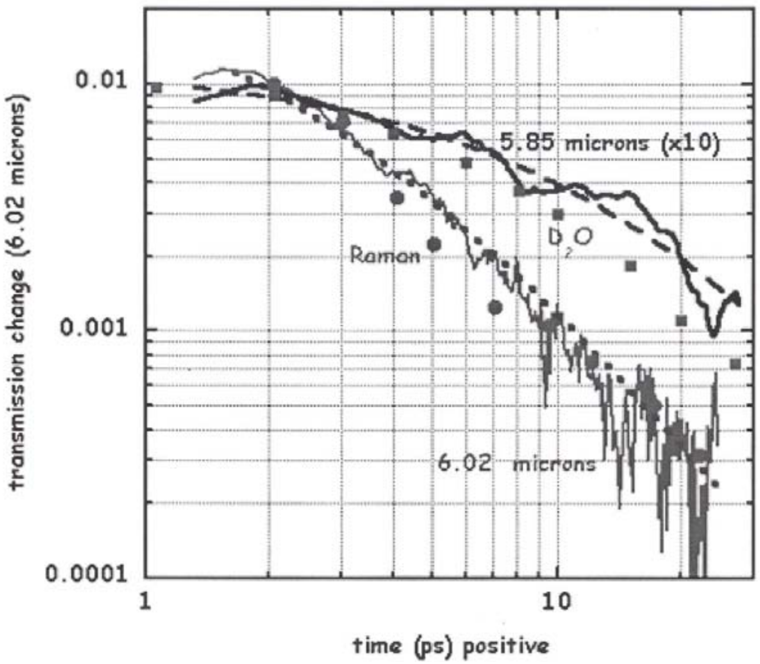
Phys. Rev. Lett. **88**, 135501, 2002
Phys. Rev. B. **65**, 035214, 2002.
Phys. Rev. Lett. **87**, 145501, 2001
Phys. Rev. Let. **85**, 1452 2000
J. Appl. Phys. **93** 2316 2003

Major program in hydrogen vibrational dynamics

Defect	ω_H (cm^{-1})	T_1 (ps)	T_1 (ps)	ω_D (cm^{-1})
H_2^*	2062.1	1.9	4.8	1500.1
IH_2	1987.1	12	20	1446.5
IH_2	1990.0	11	18	1448.7
VH_2	2122.3	60	70	1547.9
VH_2	2145.1	42	55	1565.1
VH_4	2223.0	56	143	1617.5
$HV{\cdot}VH_{(110)}$	2072.5	295	93	1510.4

Protein Dynamics with FEL sources



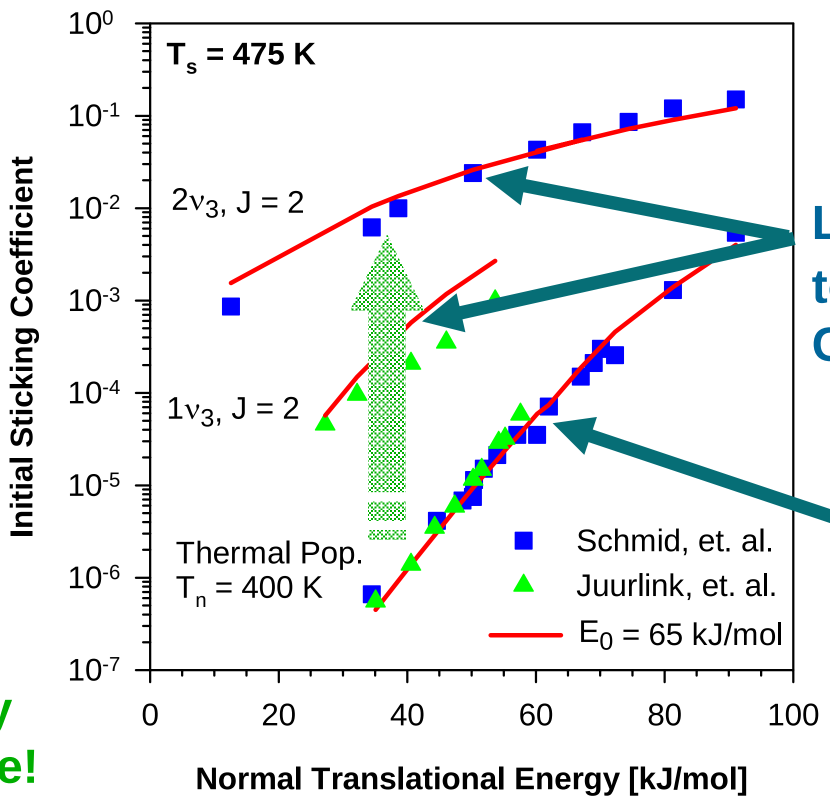


powerlaw decay: $(t/\tau)^{-2}$, τ = 2.1 ps at 6.02 um, 15 ps at 5.8

Dynamics of myoglobin Amide I ($CONH_2$) band.
Felix FEL replicated at J-Lab.

A. Xie, L. van der Meer, W. Houff, R.H. Austin Phys. Rev. Letts. 84 5435, 2000

The benefits of high repetition rate and tunability



Laser tuned to ν_3 antisymmetric C-H stretching vibration

No laser

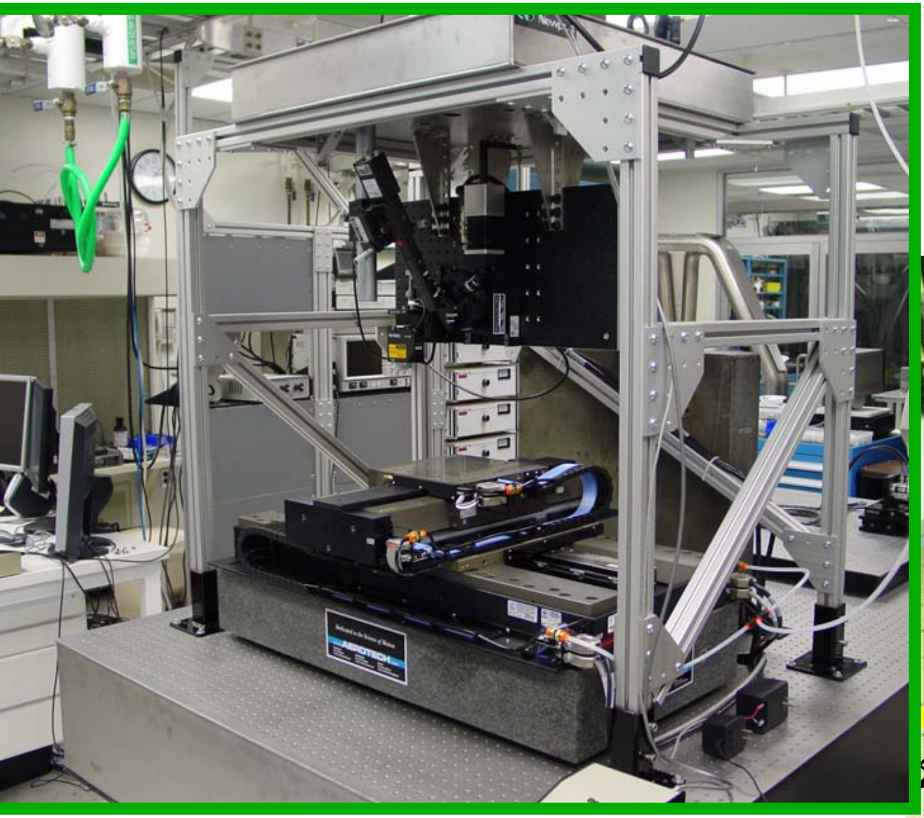
IR-laser pumping increases reaction probability by many orders of magnitude!

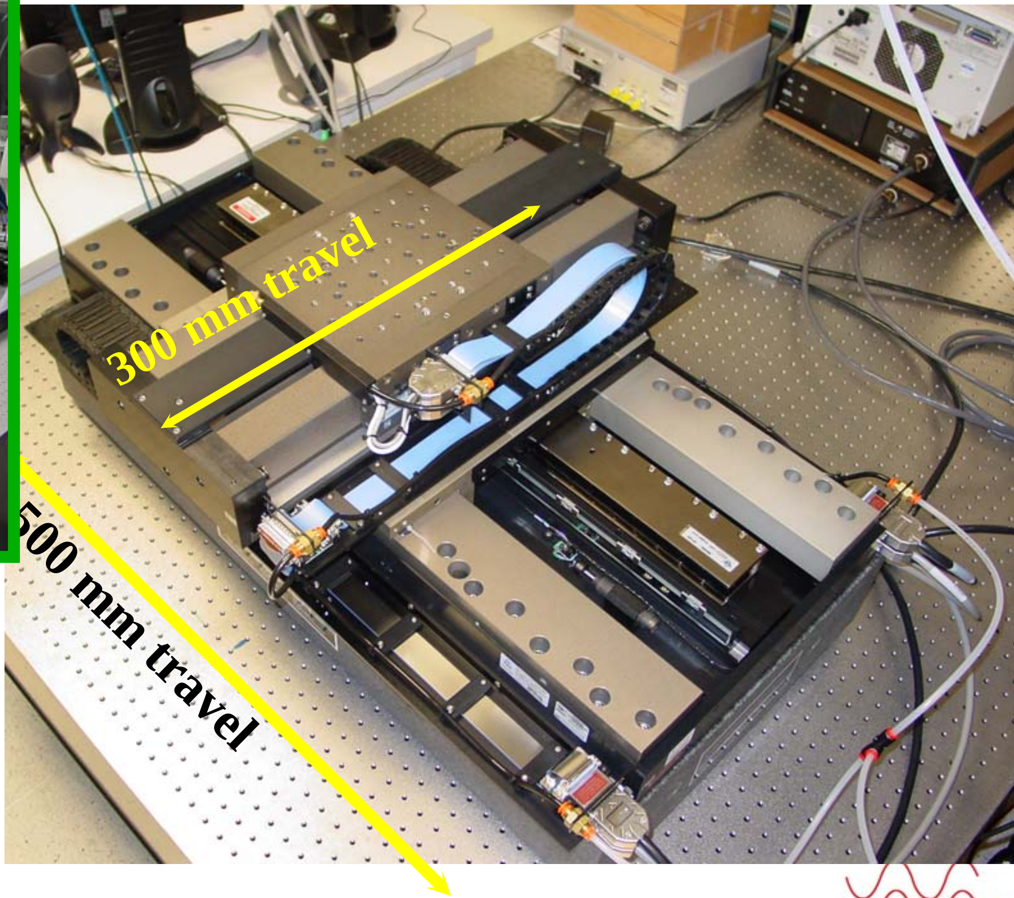
Dissociative chemisorption of a CH_4 molecular beam incident on a Ni(100) surface with and without laser excitation of the.

Ian Harrison, UVa
Microcanonical Unimolecular Rate Theory at Surfaces – IR Photochemistry in Catalysis

Prototype Laser Microengineering Station for UV FEL

- First 3D laser microfab. station
- State-of-art speed, resolution, and processing area (+/- 0.25m)





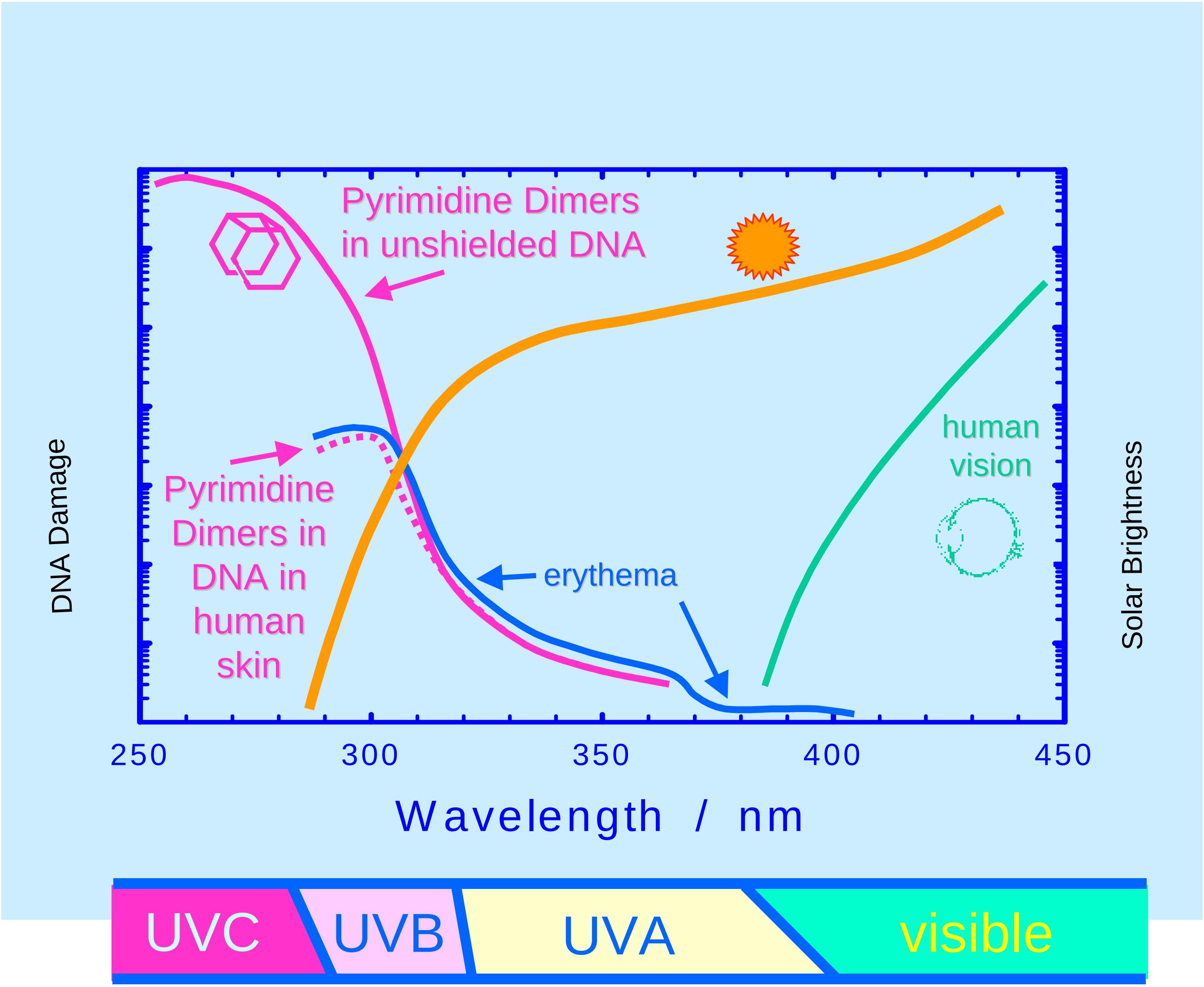
- Designed and built by Aerospace Corp. Installed in User Lab 4

UV Photodamage: The Need for a High Power UV/Violet Light Source

ASP Study Group: details from John Sutherland

- Determine photo damage probabilities as a function of wavelength for:
  - Photochemical Modifications of DNA
  - Immunological Effects
  - Induction of Basal and Squamous Cell Carcinomas (Mice)
  - Cutaneous Malignant Melanomas

Courtesy of John Sutherland, East Carolina University



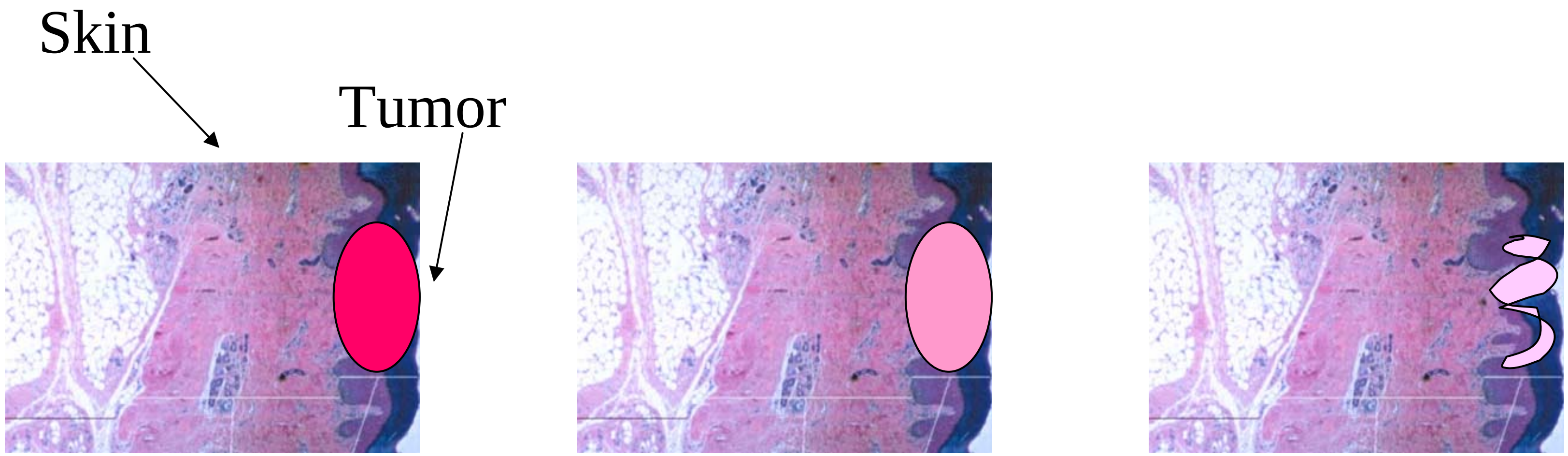
Courtesy of John Sutherland, East Carolina University

Photodynamic Therapy (PDT)

- Well-established cancer treatment for accessible, non-metastatic tumors
  - Match-up of laser output wavelength (color) with absorption line of a vital biological dye
  - Dye must be preferentially absorbed by target organ (typically skin and lung cancers)
  - Dye must have no other serious health effects and be FDA approved
  - very few dyes meet all requirements (i.e., “photofrin”)

Courtesy of Harvard and EVMS

Photodynamic Therapy (PDT)



Preferential absorption of dye by tumor

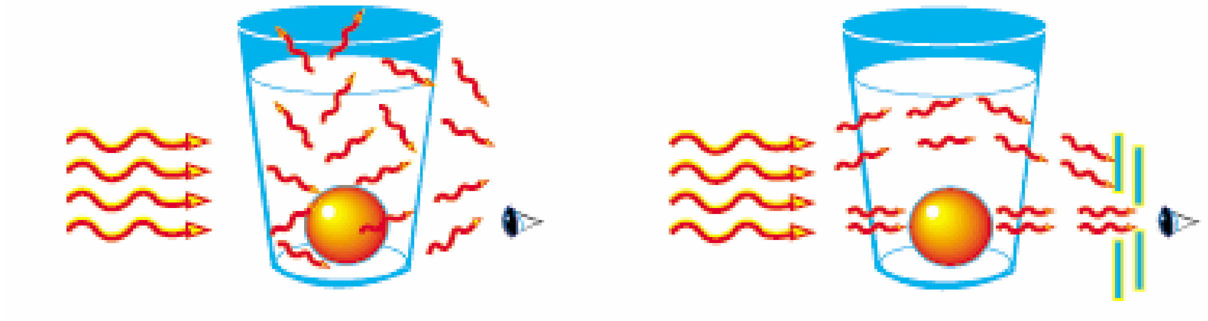
Irradiation by laser absorbed by dye

Tumor cells preferentially killed

Courtesy of Harvard and EVMS

Ballastic Imaging

- Based on the use of short-pulse lasers to illuminate a complex subject and fast-gated detectors to image only the light reflected from a specified plane



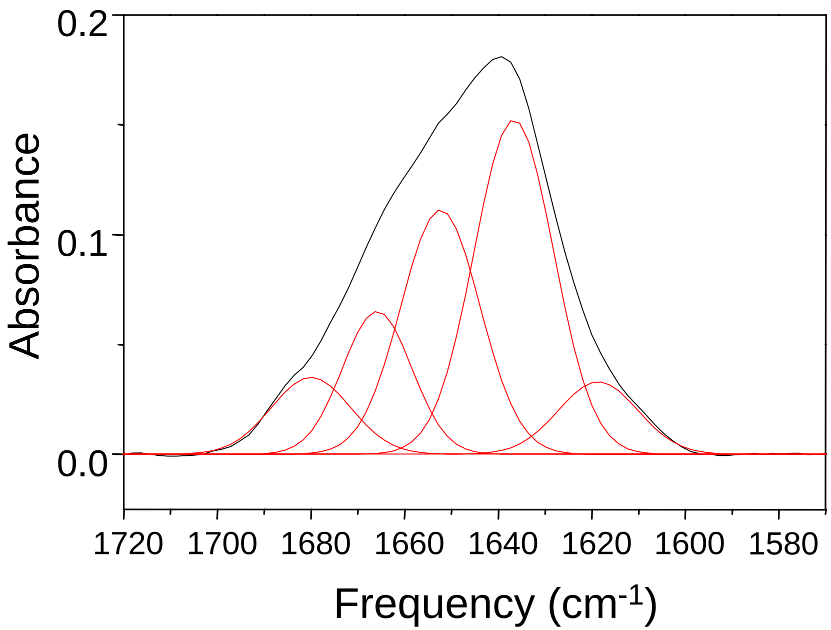
- Broadly tunable, sub-ps pulse, high repetition rate (MHz) FELs would extend this technique to a variety of complex materials

- Especially useful for medical imaging because of the transmissivity of red-near IR light in tissue

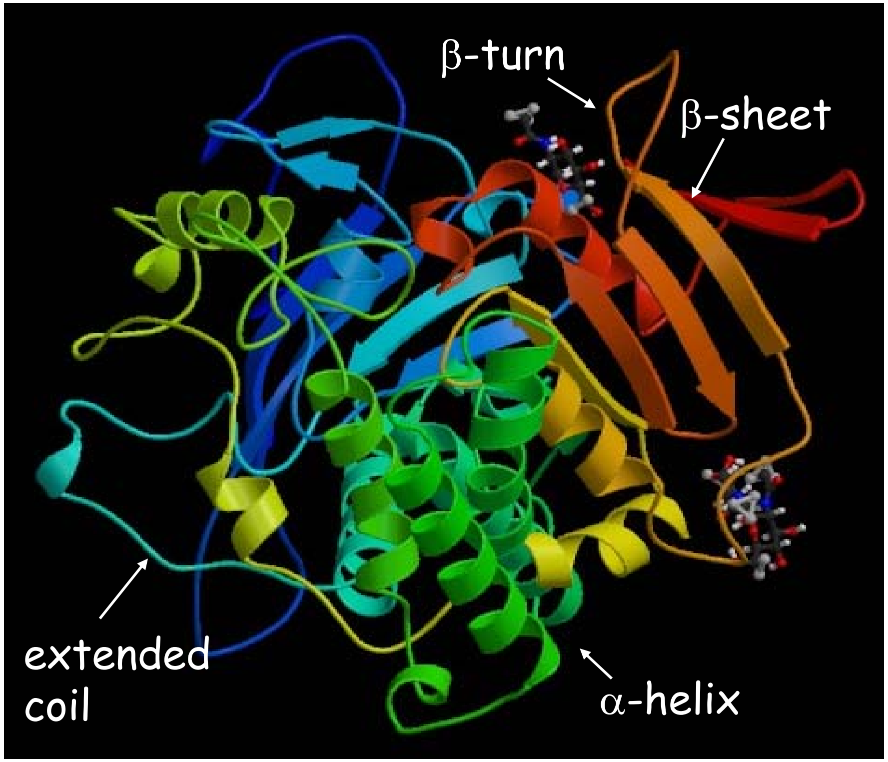
- *Reference: *L. Wang, et al., Science 253 (1991), 769

Protein Structure / Dynamics

Amide I Secondary Structure Assignments:	
1620 - 1640	β-sheet
1644	extended coil (D_2O)
1648 - 1657	α-helix
1665	3_{10} helix
1670 - 1695	anti-parallel β-sheet, β-turn



Carboxypeptidase

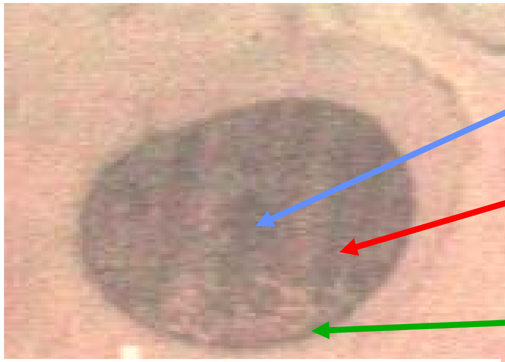


IR MICROSPECTROSCOPY OF CAUCASIAN HAIR

P. Dumas, L. Kreplak, F. Briki, J. Doucet, Y. Duvault, F. Leroy, D. Saint Léger

J.L. Leveque, L. Miller, G.L. Carr and G.P. Williams

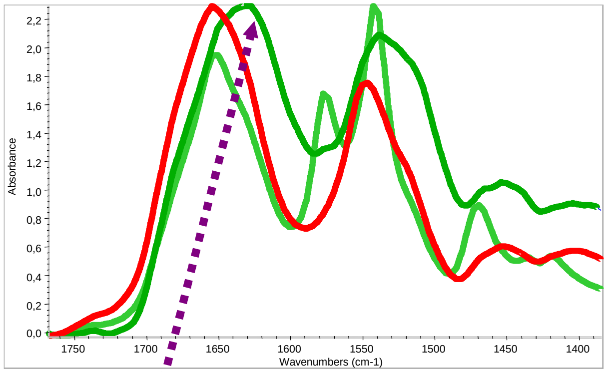
Optical image

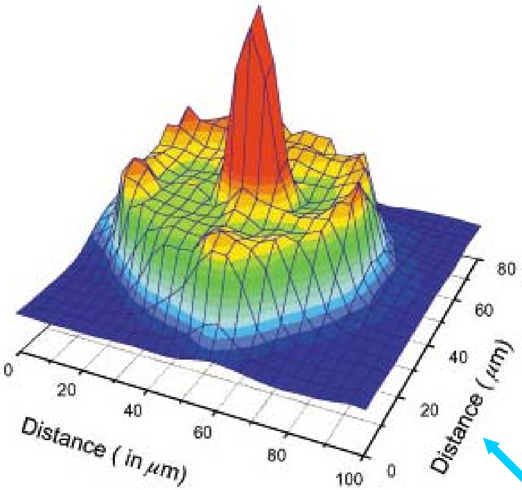


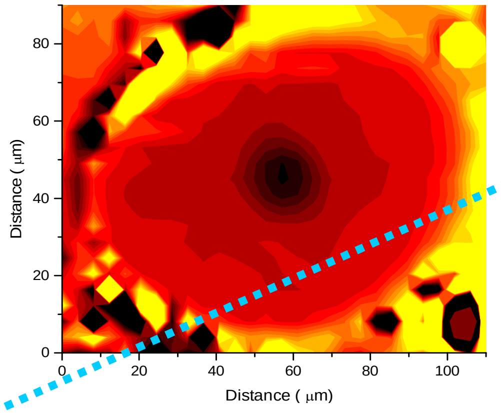
1=medulla

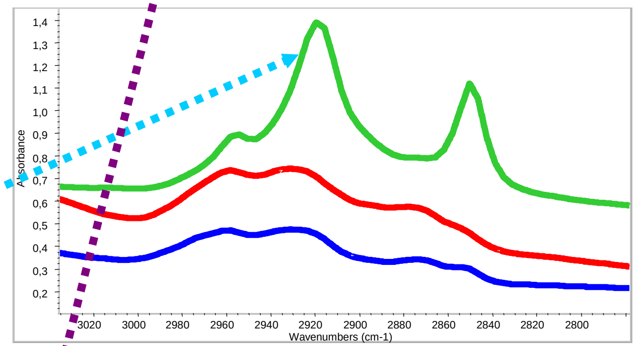
2 = cortex

3= cuticule









Lipids 2919 cm^{-1}

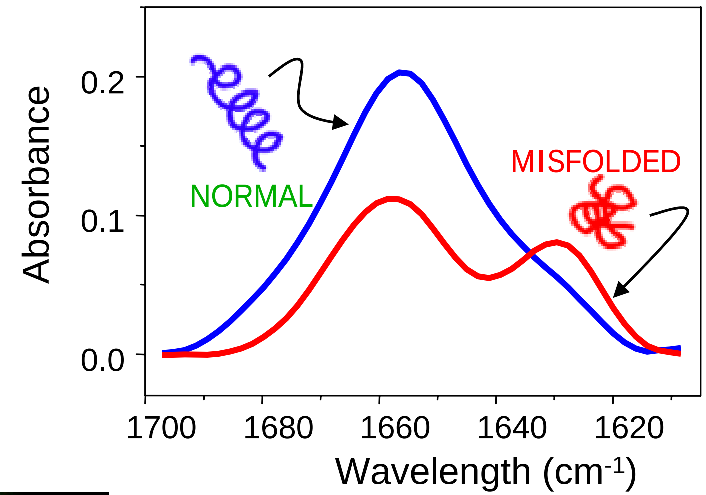
β–sheet protein at cuticle

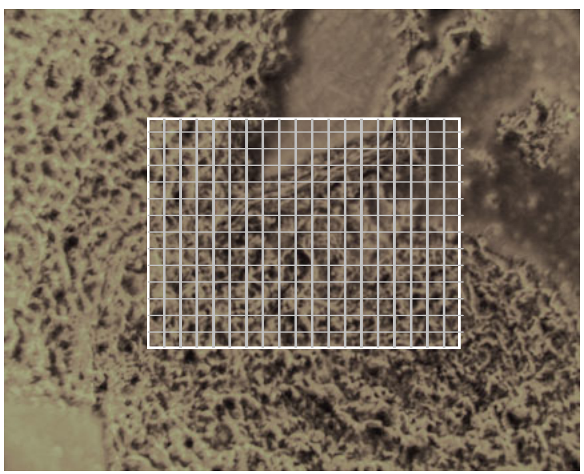
Alzheimer's Disease Plaques

J. Miklossy, L. Forro (Swiss Univ. Inst. Of Pathology) and L. Miller (NSLS)

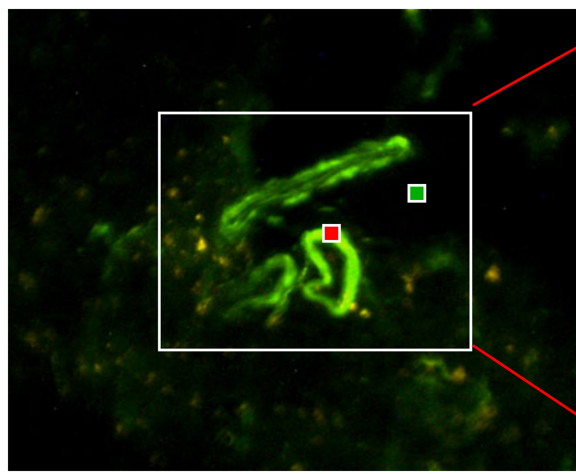
Alzheimer's plaques are misfolded β-amyloid protein

- α-helical protein cleaved and folds to β-sheet format
- plaques are thought to damage surrounding neurons

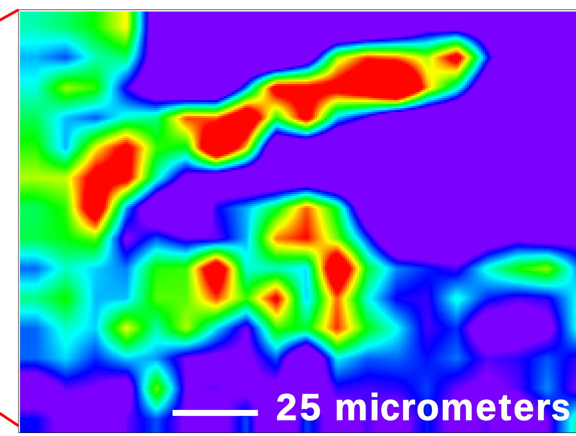




visible light image



fluorescent light image

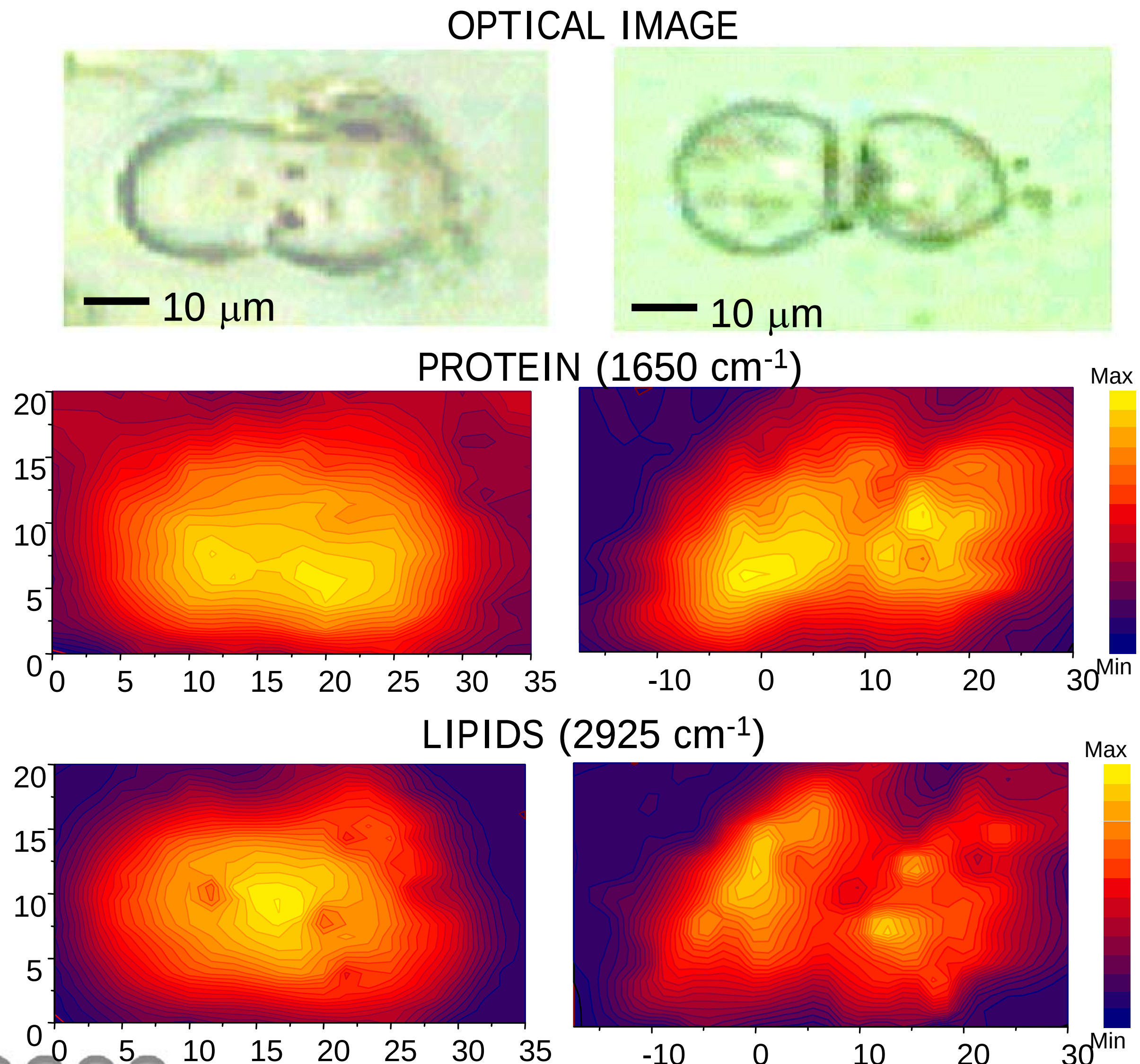


infrared light image

L.M. Miller, P. Dumas, N. Jamin, J.-L. Teillaud, J. Miklossy, L. Forro (2002). *Rev. Sci. Instr.*, 73: 1357-60.

Chemical Imaging of Mitotic Cells

N. Jamin, P. Dumas (LURE), J.L. Teillaud (Institute Curie), G.L. Carr, G.P Williams (NSLS)



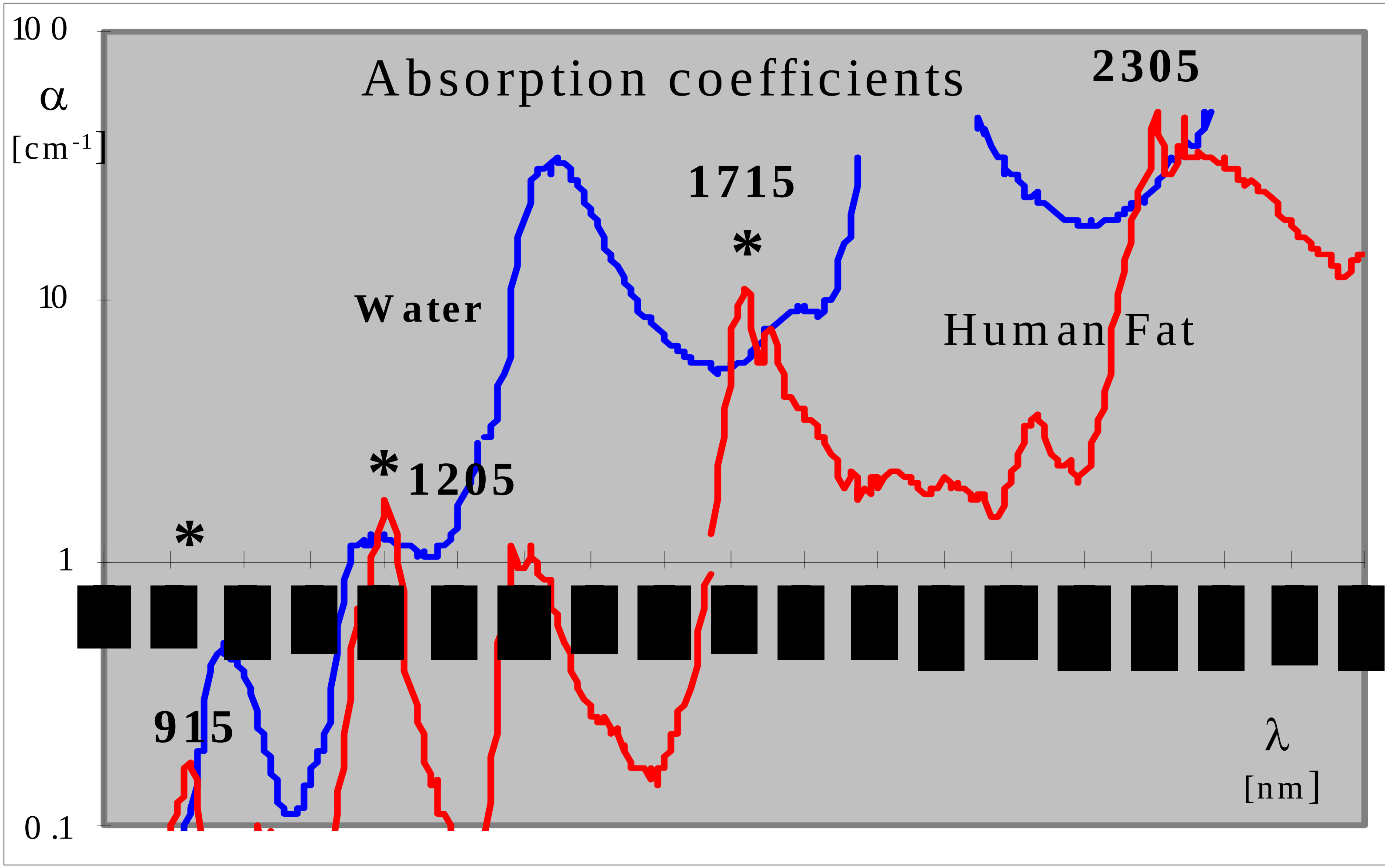
N. Jamin, J.L. Teillaud, P. Dumas, G.L. Carr, G.P. Williams *Proc. Natl. Acad. Sci.* ***95*** *4837 (1998).*

Laser Bioscience Center - Opportunity

Research & Application Opportunities with FEL capabilities:

- Diagnostics of cancers and diseases
- Photodynamic therapy of cancers at 10 times currently possible rates
- Phototherapy of skin disorders
- Biomedical imaging with short pulse, tunable, non-ionizing, laser light
- Protein sorting, gene expression studies with laser-mass spectroscopy
- Studies of ultraviolet damage to biological systems from DNA to mammals
- Multimodality (nuclear combined with X-ray and optical) imaging for biomedical research

Fat Water



Courtesy: R.Anderson, Harvard MGH

Laser Bioscience Center - Proposal

- A Laser Bioscience Center wing at Jefferson Lab's FEL User Facility.
- Design and Construct 26,000 sq. ft. Laser Bioscience Center User Facilities.
- Cost: ~$6M

- Mission of LBC: To utilize the unique capabilities of Jefferson Lab's FEL and expertise in biomedical imaging in bioscience research, biomedical and biochemical applications, small animal imaging, medical imaging, disease diagnostics and treatment.

- Modeled after similar NIH funded laser science centers at MIT and Harvard-Mass General Hospital.
- Key outside Principal Investigators from the UVA Medical Sciences Center and the Wellman Lab for Photomedicine at Harvard Univ. will solicit core operations funding from NIH, et al.

- Regional participants:
  - Proteomics Consortium (Eastern Virginia Medical School, The College of William and Mary, and Incogen, Inc.)
  - The research institutions in the Hampton Roads Research Partnership
- At this time the Proposal is supported by University of Virginia, Harvard Medical School, Princeton Univ., East Carolina Univ., City of Newport News, The College of William and Mary, Eastern Virginia Medical School, Hampton Roads Research Partnership (HRRP), Hampton Roads Partnership (HRP).
- Developed from Virginia Gov. Warner's Biotechnology Commission (2003).

Summary

JLab FEL Upgrade is on line as a user facility with THz, IR, and (soon) UV light

- Broadly tunable
- Sub-picosecond pulses
- Excellent beam quality
- Unmatched power, pulse energies
- (also have conventional lasers synchronized with FEL)

- Initial studies using the IR Demo FEL and pioneering work at the Stanford, Vanderbilt, Duke, ALS, BNL et al have shown the utility of high brightness light sources for bioscience activities
- Proposals under development from this workshop should lead to expanded capabilities for applying FEL capabilities to biological and biomedical problems

Laser Bioscience Center Proposal Collaborators

- A. Gomez, University of Virginia (Co- PI)
- R. Anderson, Harvard Mass. General Hospital (Co- PI)

- R. Austin, Princeton University
- J. Sutherland, East Carolina University
- J. Semmes, Eastern Virginia Medical School
- W. Cooke, The College of William and Mary
- D. Manos, The College of Williams and Mary
- W. Wasilenko, Eastern Virginia Medical School
- L. Beach, Hampton Roads Research Partnership

"Many Hands Make Light Work"- Erasmus c.1330

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Trey Thurman*
Dawn Venhaus *
Richard Walker
Mark Wiseman

Byung Yunn
Shukui Zhang
Richard Evans
Charlie Sinclair
Gwyn Williams
+ Alan Todd
+ John Rathke
+ Hans Bleum
++ Bill Colson
**Anne Reilly
***Henry Helvajian

*Alumni ,**CWM
+ AES, ++ NPS
***Aerospace

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