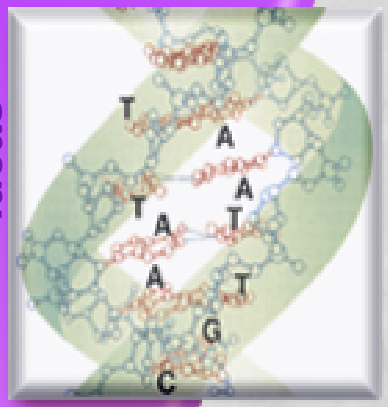
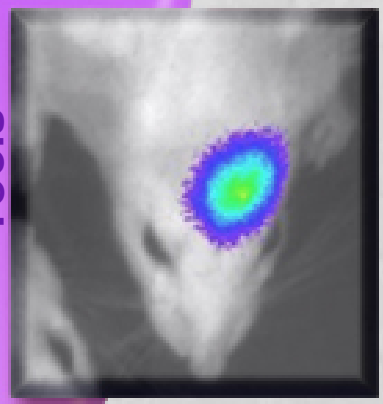
People

Ideas



Tools



"Shedding Light on Life©"

CBST

CENTER for BIOPHOTONICS SCIENCE and TECHNOLOGY

Applications of Biophotonics to Bioscience and Medicine

Dennis L. Matthews, PhD
Director NSF-CBST – UCD/LLNL

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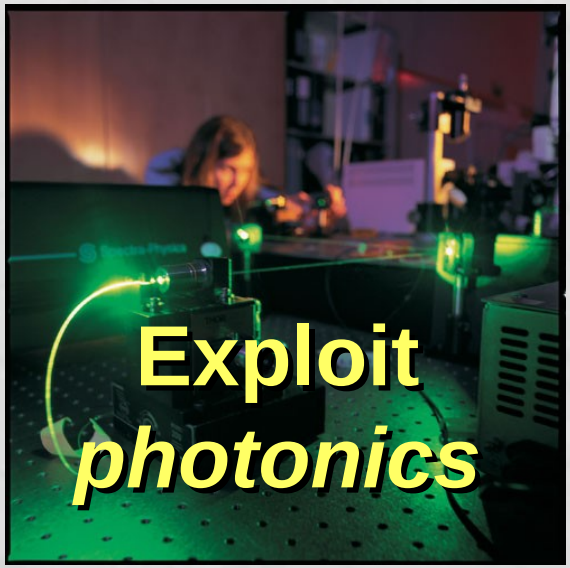
Work supported by the National Science Foundation Cooperative Agreement No. PHY-0120999 and Match Funds from Participating Institutions

UCDAVIS

Mission of the NSF Center for BioPhotonics Science and Technology

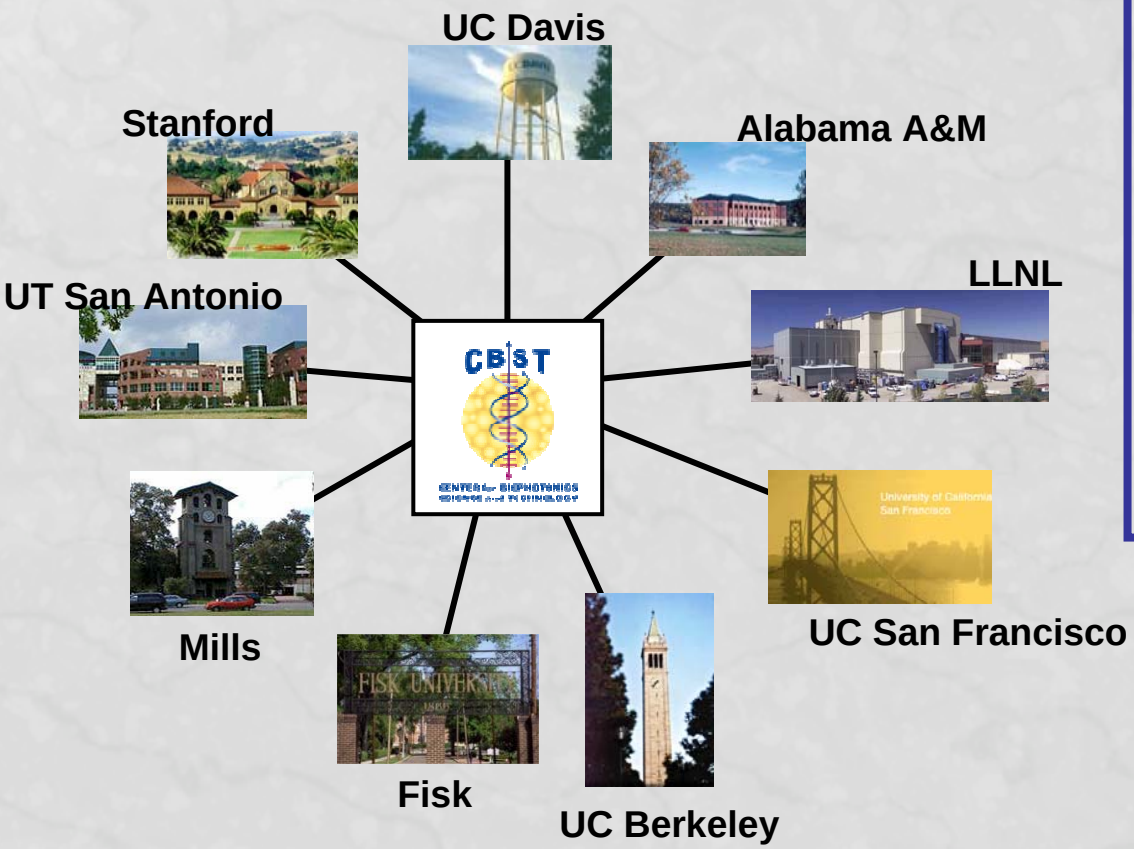


To address grand challenges in life sciences, bioengineering, national security and medicine

- Molecular scale detection and imaging in living organisms
- Molecular structure determination of protein complexes
- Discovery of the triggering mechanisms of disabling diseases
- Finding single abnormal cells among healthy ones – surgery at the cellular level of precision
- Development of NON INVASIVE Medical Tools

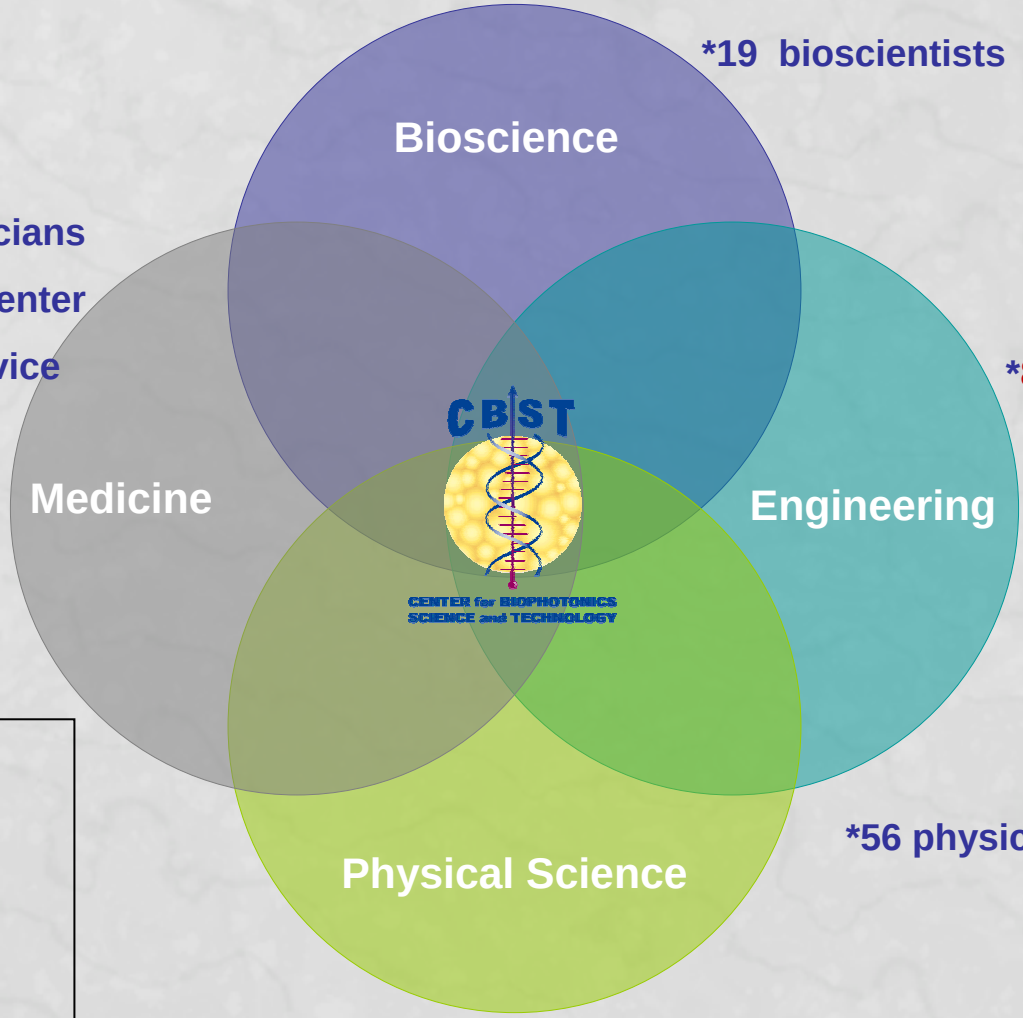
Primary Objective of the CBST S&T Program

To establish ***teams*** of researchers and the resources to produce ***scientific breakthroughs*** that make a major impact in biophotonics especially in the areas of *bioimaging*, *biomaterials*, *medical applications*, *bioassays*, and *biosensors*.



- **Projects must be interdisciplinary, multi-institutional, integrative – science, education, commercial potential**
- **Center must produce high impact outcomes in science, education, commercial products**

We Emphasize Interdisciplinary Team Science



*19 bioscientists

*11 research physicians

CBST HQ at Med Center

2 affiliated Med Device startup companies

*8 engineers

*56 physicists, chemists

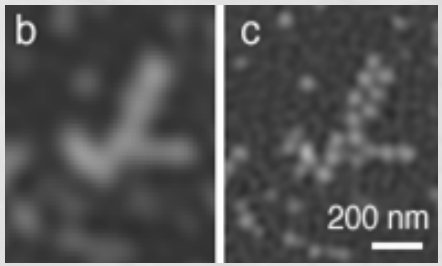
UG/G students

Engineering: 24
Physical Science: 49
Biological Science: 17
Computer Science: 1
Business: 6
Human Development: 16

* MD, PhD, and MD/PhD faculty

Programs and Highlights

Science and Technology



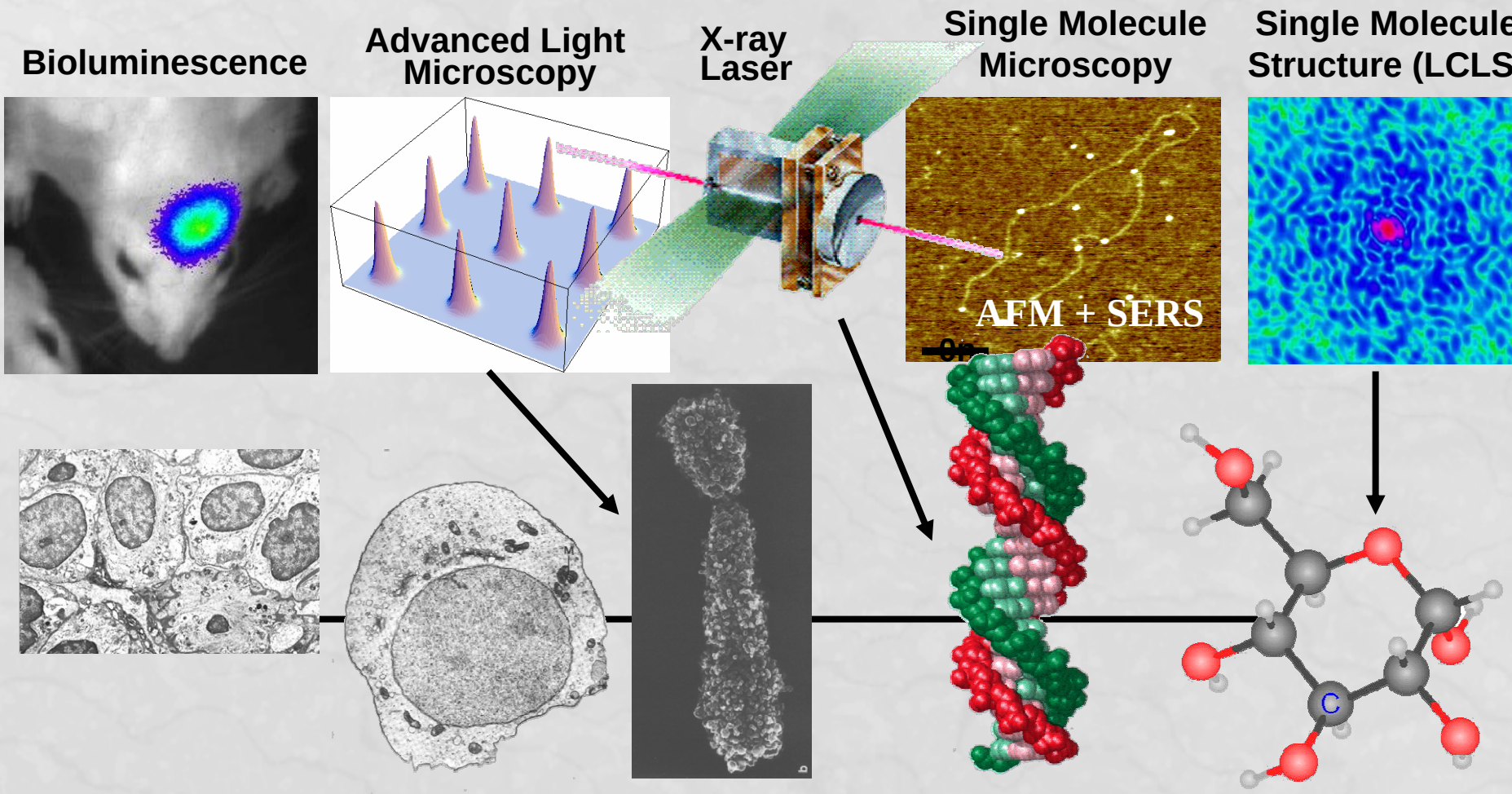
Education, HR Development

Management

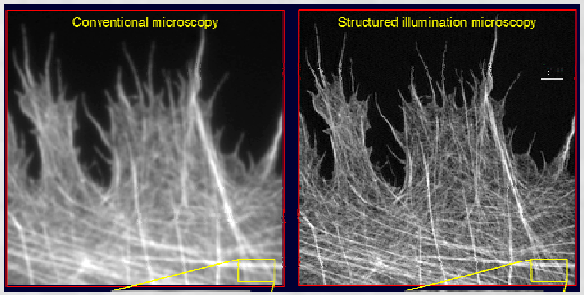
Diversity

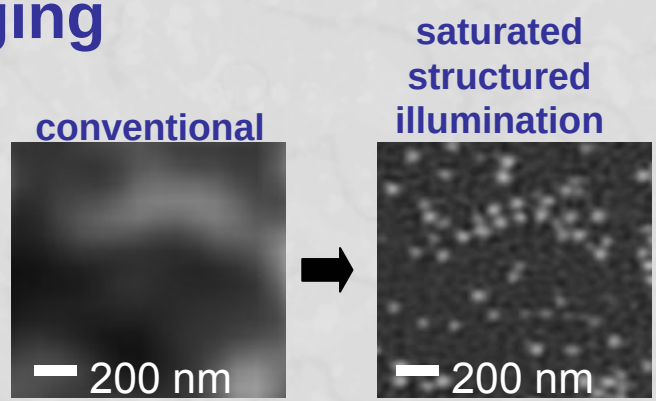
Knowledge Transfer

CBST is all about imaging/detection from cell clusters to biomolecules



Bioimaging



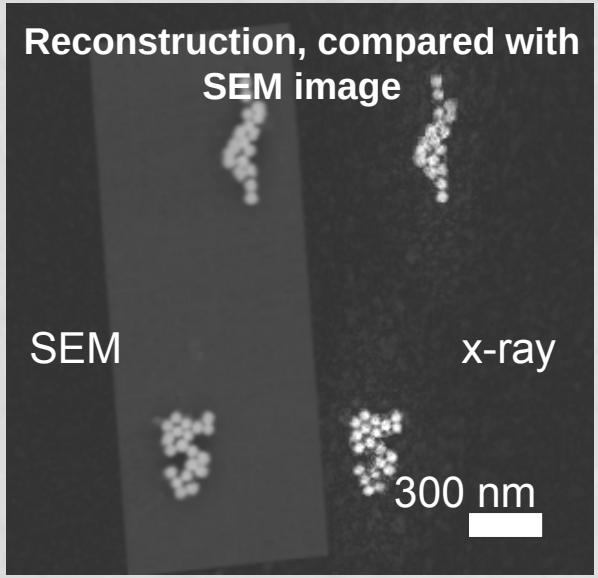


- **ADVANCED OPTICAL IMAGING**

  Light microscopy beyond the classical resolution limit

  5 yr Goal: Demonstrate viability of structured illumination for biological imaging.

Center Highlight: 46 nm resolution from 532 nm illumination (5X diffraction limited resolution!)



- **ADVANCED X-RAY IMAGING AND DIFFRACTION IMAGING**

  Biological applications of the LCLS x-ray source

  Novel water-window cellular imaging using tabletop x-ray lasers

  5 yr Goal: A) Establish feasibility of single molecule x-ray structure determinations. B) Demonstrate feasibility of table-top x-ray laser cellular imaging.

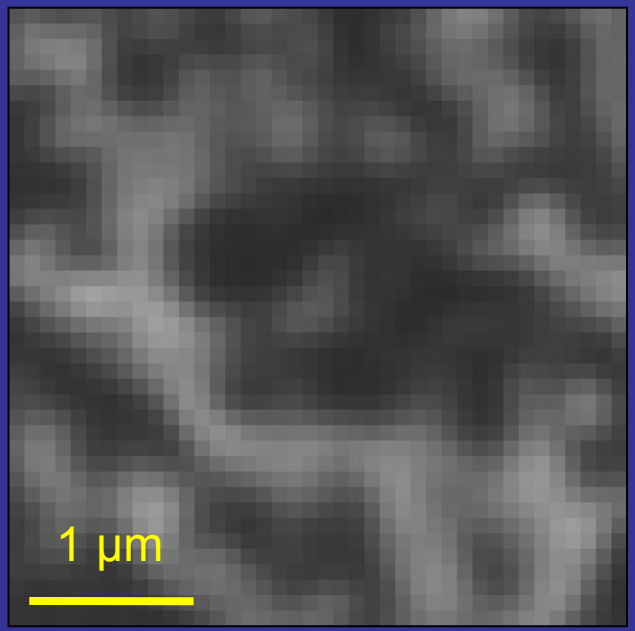
Center Highlight: First demonstration of lenless x-ray imaging (20 nm resolution)

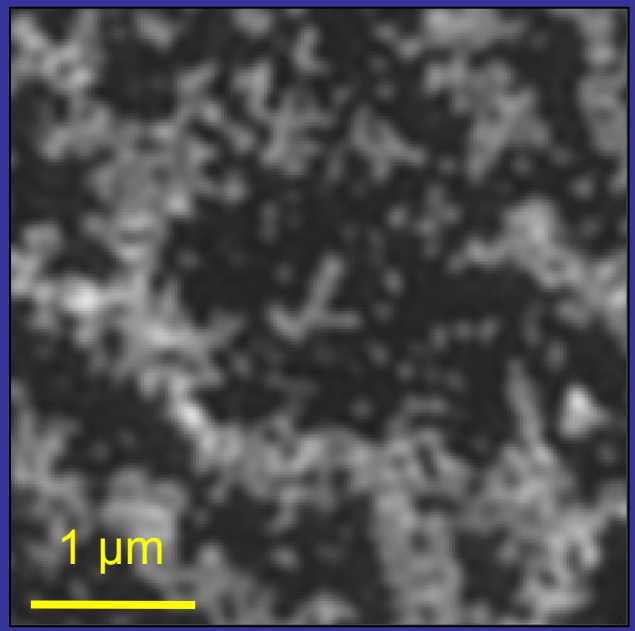
Non-linear structured illumination works!

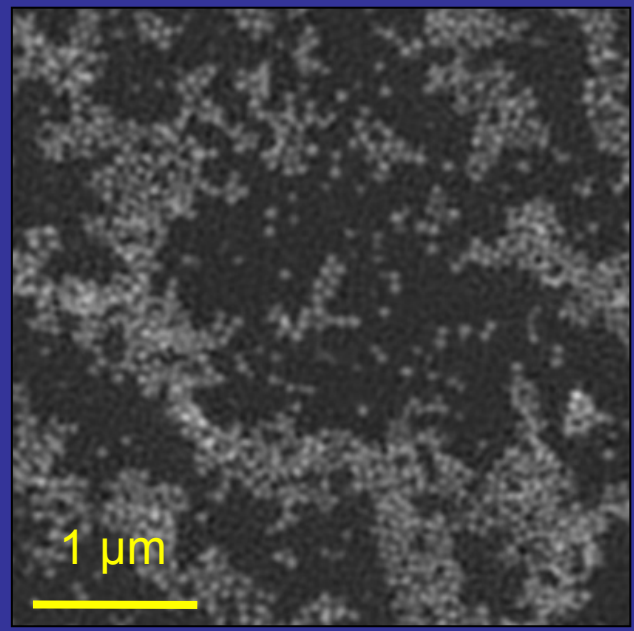
Conventional microscopy

Linear structured illumination

Saturated structured illumination







~250 nm resolution (diffraction limit)

46 nm resolution with 530 nm illumination- 5x diffraction limit!

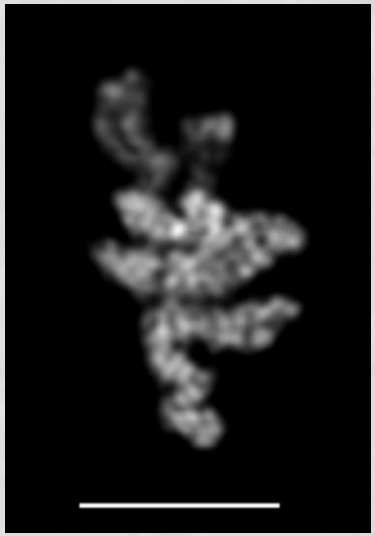
50 nm microspheres

Biological imaging: S. pombe Chromosomes

Conventional microscopy

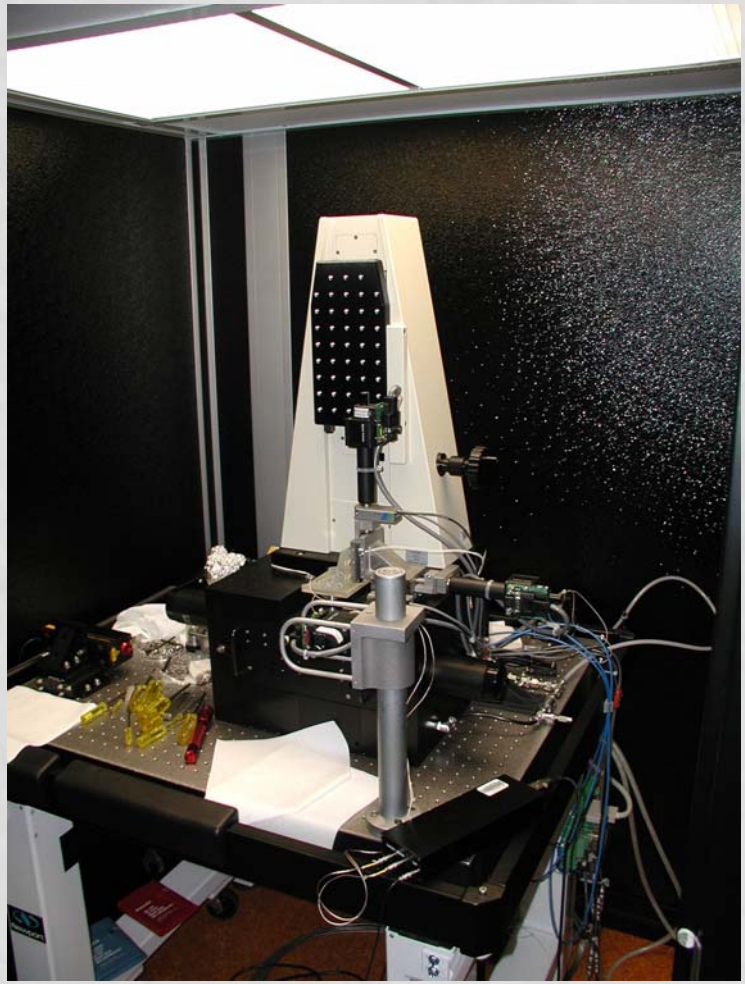
nda3 mutants (prophase arrest)

Structured illumination



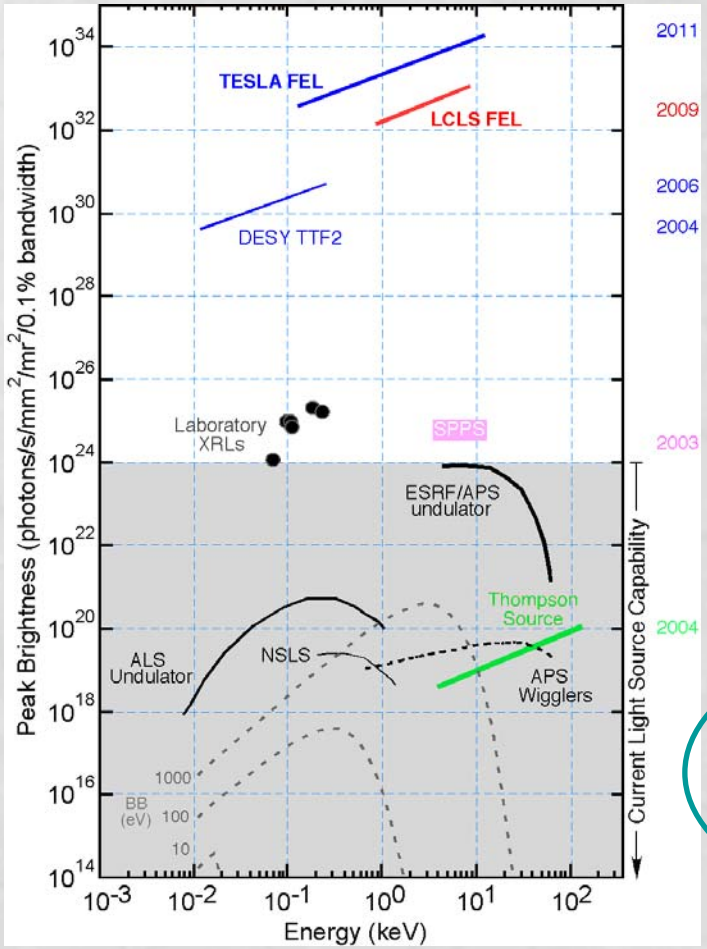
Scale bar: 2μm

OMX

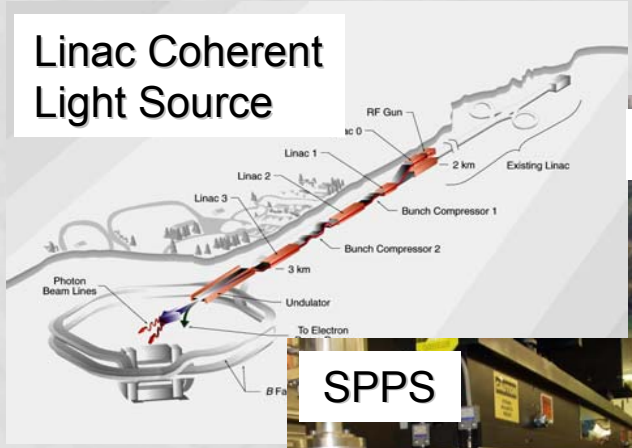


- **Fast data acquisition with 4 wavelengths simultaneously**
- **Stage movements by piezo electric devices**
- **Structured illumination technology**
- **CBST will distribute 10 of these microscopes to bioscience community for evaluation**

We are entering a new era in x-ray science



Linac Coherent Light Source

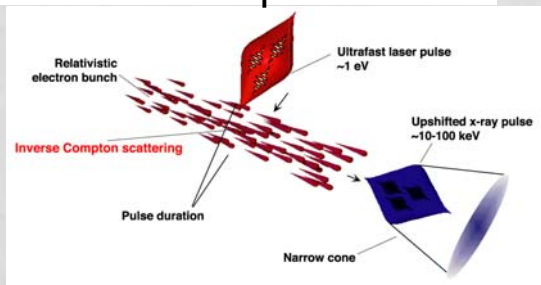


Tesla Test Facility

SPPS

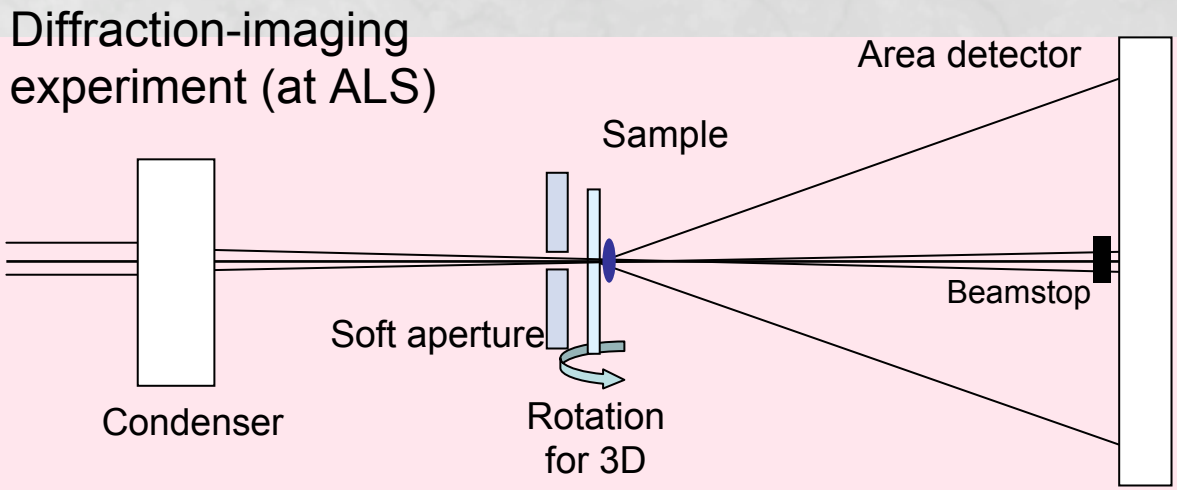
- femtosecond
- 10^{13} photons
- Angstrom wavelength

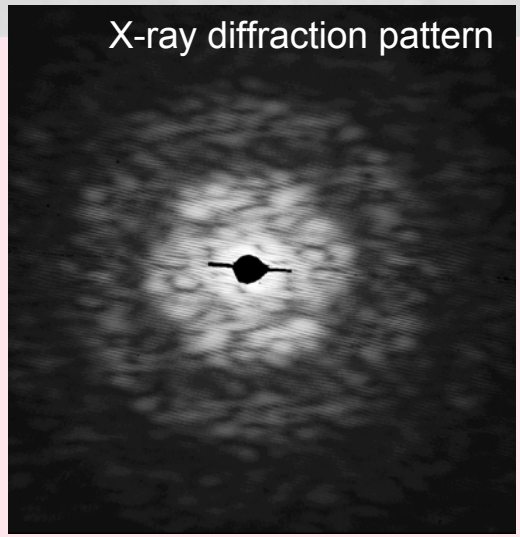
LLNL Thompson source



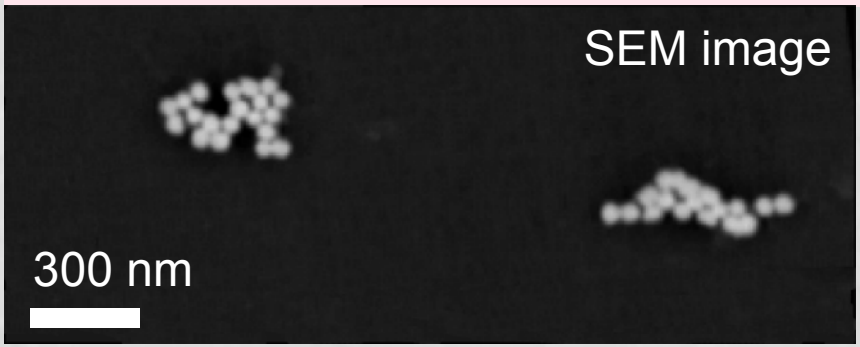
This short-pulse high-fluence x-ray regime is completely unexplored. What ever we do with these sources will be new science

Lenless x-ray imaging has produced resolutions of 10 nm using complex test objects and 2 nm synchrotron radiation

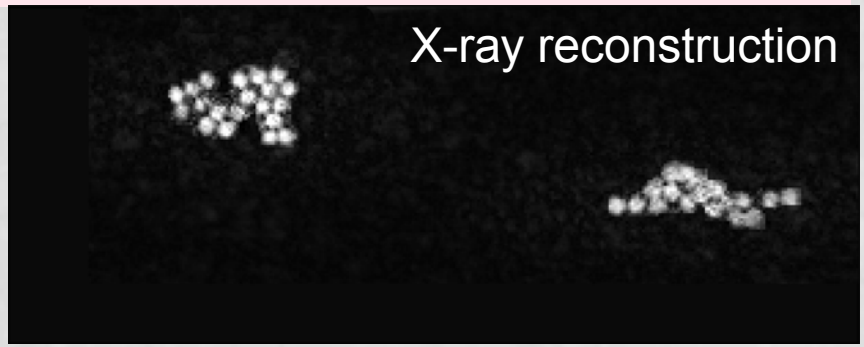




λ = 2.1 nm, Rayleigh resolution = 10 nm



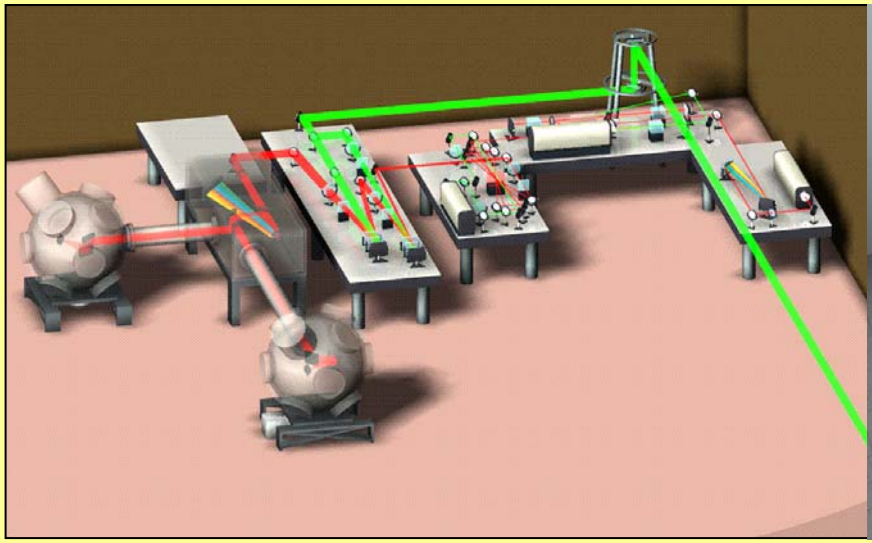
Sample: 50 nm gold spheres



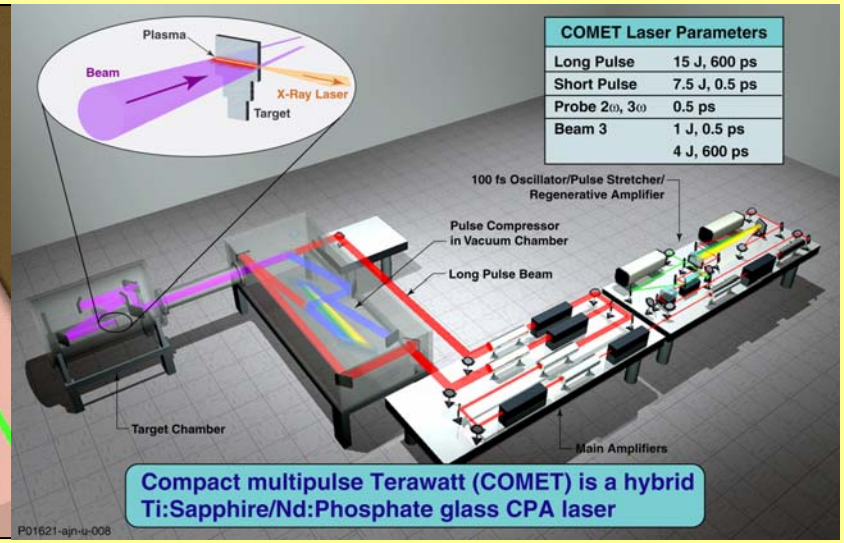
Reconstruction performed with variation of Fienup algorithm, with dynamic support constraint

Appendix II: X-ray laser experiments have been conducted at several LLNL Laser Facilities

JANUSP



COMET



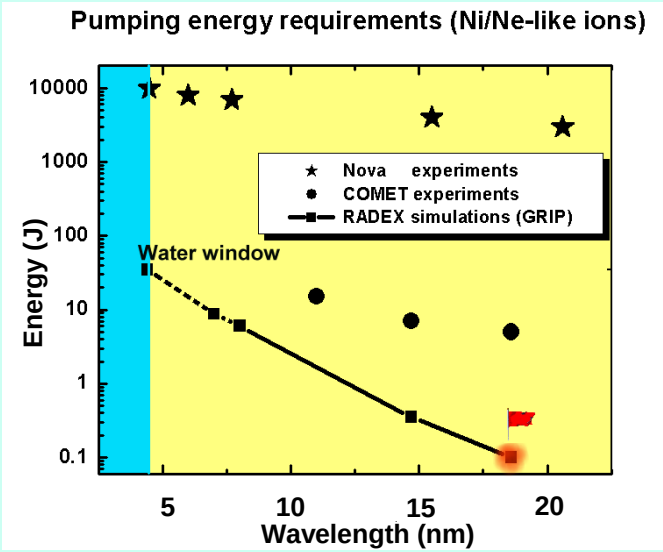
Wavelength, t:	**800nm, 80 fs**		**1054 (527) nm, 500fs - 30 ps**
Energy @ 1ω :	**120 mJ @ 10 Hz**	**15 J @ 2 shots/hr**	**7.5 J @ 1 shot/ 4min**
Intensity*:	**6 x 10^{14} W cm^{-2}**	**5 x 10^{16} W cm^{-2}**	**5 x 10^{15} W cm^{-2}**
X-ray laser:	**18.9 nm @ 10Hz**	**(GRIP)**	**11.9 - 46.9 nm (transverse pumping)**

***@25μm x 1 cm**

Third laser JANUS ISP (200 J in 0.5 ps, 400 J in 2 - 100 ps) available in ~2005 for water-window x-ray laser experiments

FY04 Tasks: Scaling x-ray laser to short wavelengths requires higher power laser pump, $P \sim \lambda_{XRL}^{-(4-6)}$

RADEX Predicted Parameters for GRIP X-ray Laser



Z	λ_{XRL} (nm)	λ_{pump} (nm)	E_{pump} (J)	n_e (10^{20} cm^{-3})	Status
Mo	18.9	800	0.15	1	√
Pd	14.7	527	0.4	2	Feb. 04
Nd	8.0	527	8 - 10	5	Apr. 04
Ta	4.5	?	50?	>5?	Laser*

X-ray Laser Wavelength

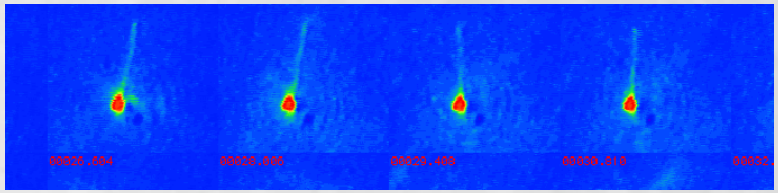
Laser Pump Wavelength

- GRIP pumping will reduce laser pump energy requirements by orders of magnitude to generate efficient x-ray laser
- Tentative extrapolation into water-window

RADEX Simulations by Shlyaptsev

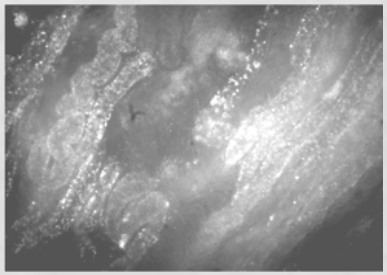
Laser* depends on JANUS ISP ~2005

Bioimaging-continued



confocal video images of a single DNA molecule interacting with an individual nuclease enzyme

- **SINGLE MOLECULE CONFOCAL MICROSCOPY**
  - *Recognition and Repair of DNA damage*
  - *DNA-protein interactions: a single molecule approach*
  - *Simulation of molecular level DNA damage and repair*
  - *Apolipoprotein E-containing lipoprotein binding to endothelium*
  - *Low energy electron interactions with water and biological systems*
  - 5-yr Goal: Discover new biology and develop new SM microscopy techniques.



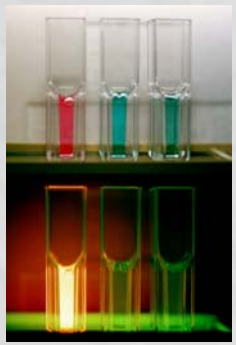
hyperspectral microscope image of human kidney tissue

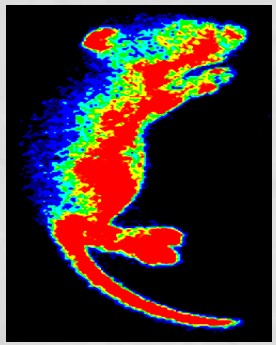
- **HYPERSPECTRAL MICROSCOPY FOR TISSUE CHARACTERIZATION**
  - *Optical spectroscopy evaluation of tissue injury*
  - *Computational studies of light interaction with cells*
  - 5-yr Goal: Discover new robust optical signatures to verify tissue viablility for transplantation

---

Near: phytochromes have a wide range of optical properties.

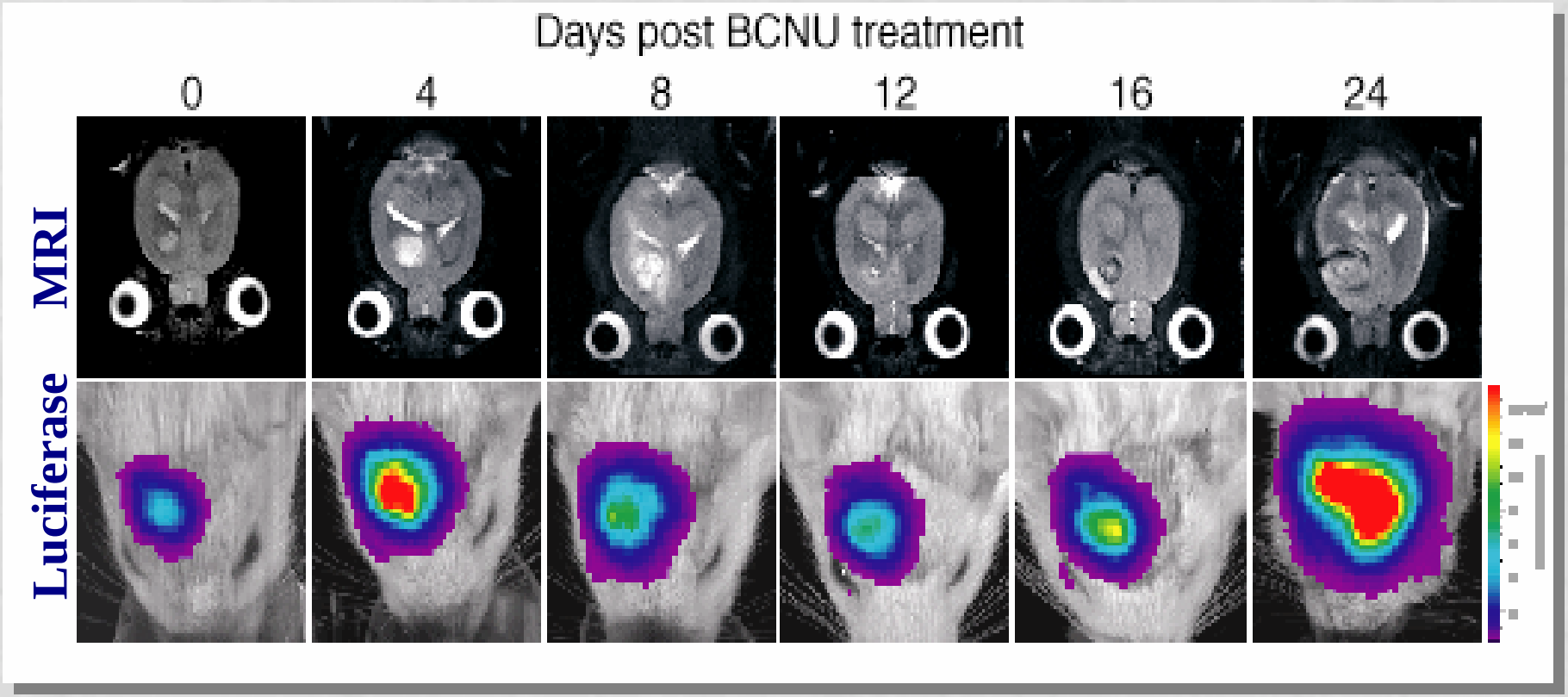
Far: *in vivo* bioluminescence luciferin / luciferase imaging





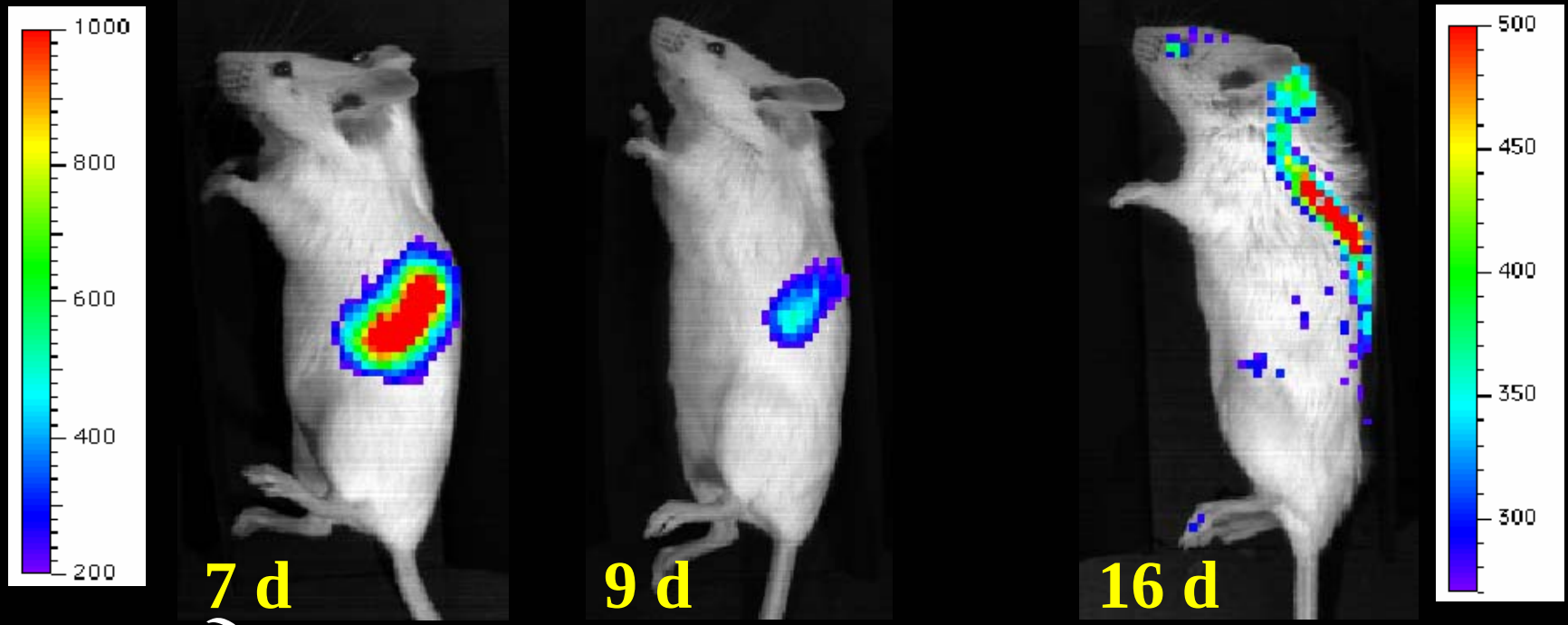
- **NOVEL OPTICAL LABELS**
  - *Phytochrome engineering in living cells*
  - *Synthesis of novel luciferyl-derivatives for use in bioluminescent assays and imaging*
  - 5-yr Goal: Develop new optical labels for imaging and biotechnology/medical assays.

Bioluminescence enables studies of the Kinetics of Tumor Growth, Regression and Regrowth



Minimal Residual Disease

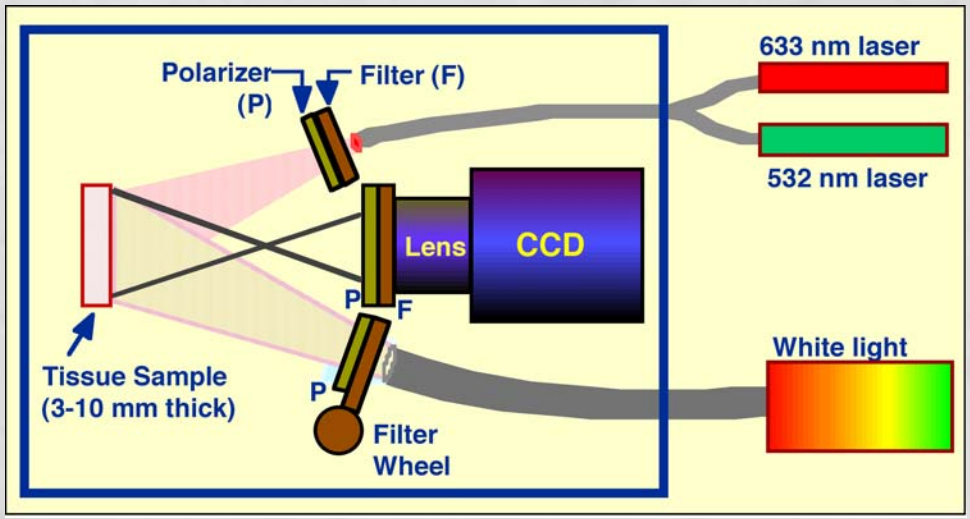
Tumor Survival after Allogeneic Bone Marrow Transplant



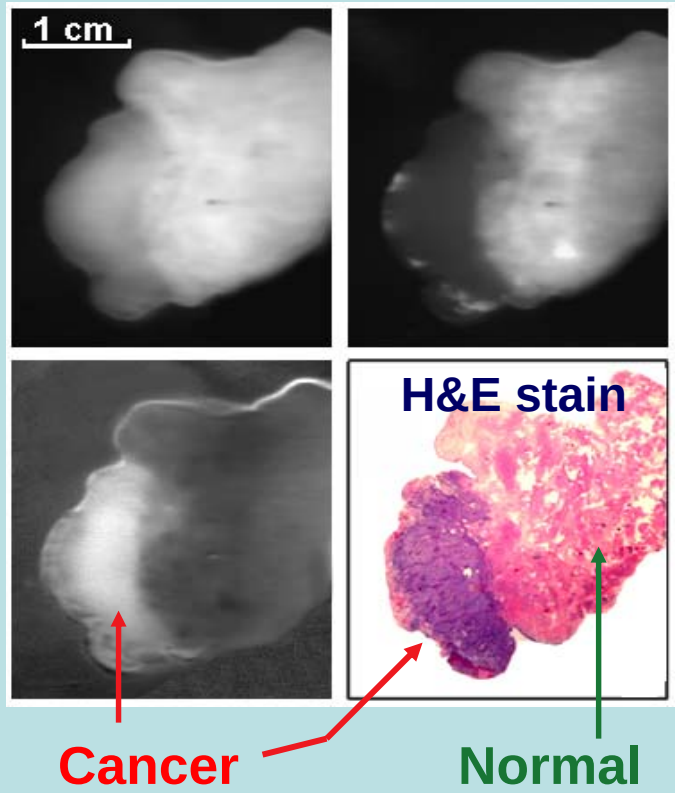
Matthais Edinger
Robert S. Negrin
Christopher H. Contag
Stanford University

Spectroscopic imaging of cancer. Application to bladder cancer

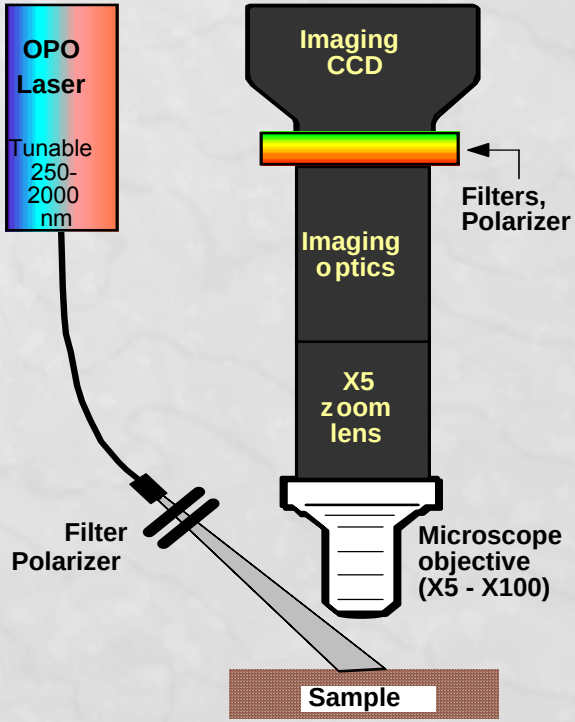
We have been developing prototypes to test novel concepts

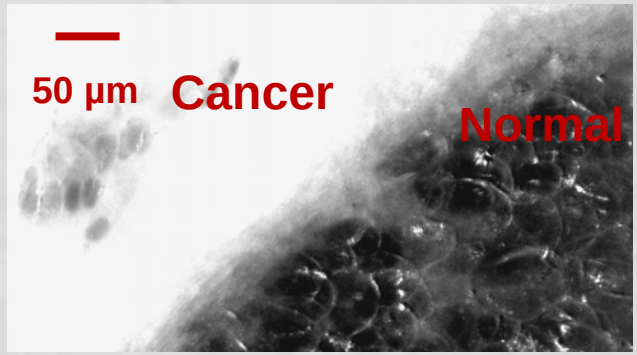


Spectroscopic images of a bladder tissue specimen containing cancer



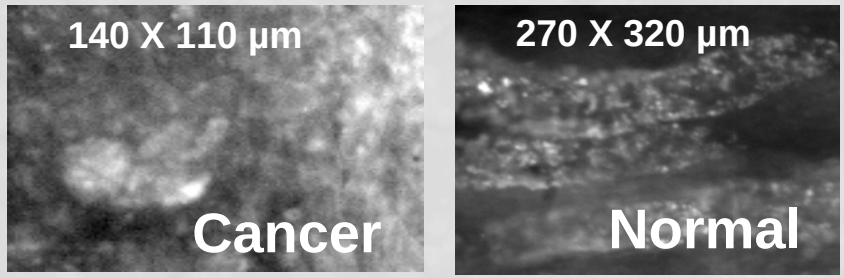
Development of hyperspectral microscopy for real time *in vivo* imaging of tissue microstructures





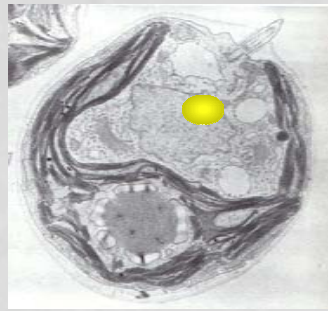
Scattering ratio images of human breast specimen (450±5 nm / 800-1000 nm)

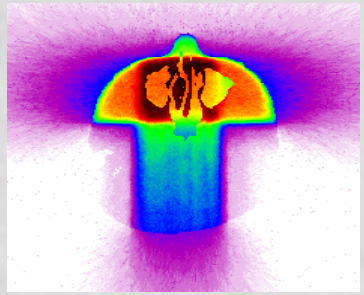
Portable Hyperspectral Microscopy System offers optimized sensitivity and multi-parameter spectroscopic imaging using polarization sensitive auto-fluorescence and light scattering.



Autofluorescence images of human kidney tubules (Ex 532 nm ; Em 700-1000 nm)

Dr. Stavros Demos (LLNL)





Brain trauma

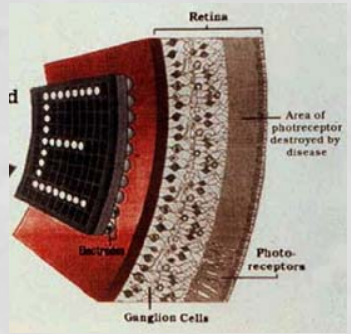
Education

Cancer Dx and Rx

Diabetes

CBST

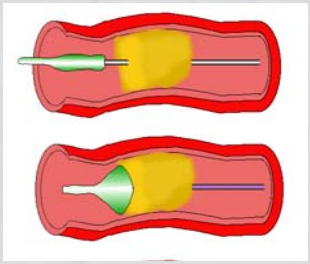
Neurostimulation implants

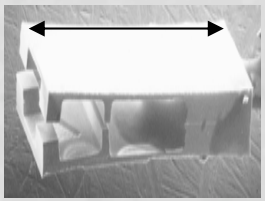


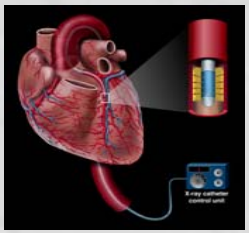
Catheter devices

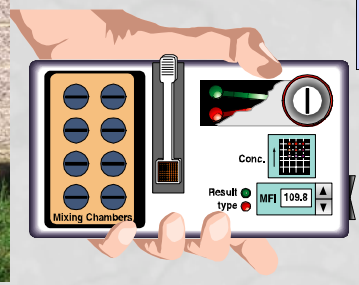
Infectious diseases

Industry partnerships









BioLuminate

Boston Scientific
Delivering what's next.

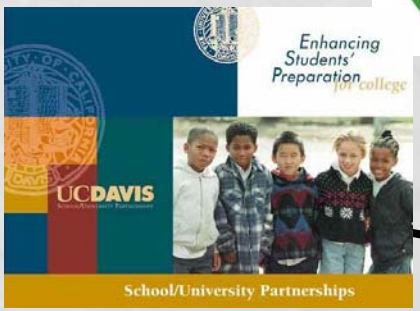
GUIDANT

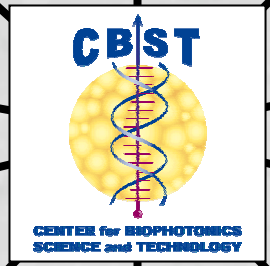
Life Wave

nomos

Medtronic
When Life Depends on Medical Technology

The CBST has multiple partners that encompass ALL areas of the Center's functions: Science & Technology, Education, & Knowledge Transfer





Focus on increasing participation of URG

people

CBST Education

Systematically Improve Science Education

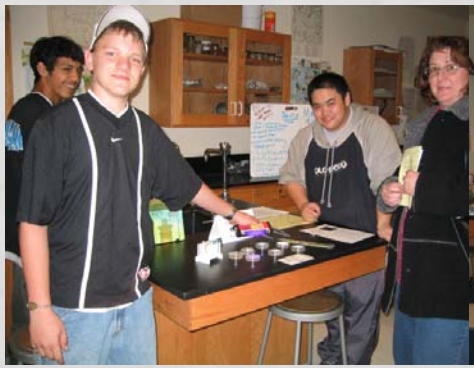
- **Increase the number and diversity of interested and eligible K-12 students**
  - After-school K-5 program - Sacramento area Child Development Center partnership
  - Year long High School research and technology training program (Center and St. Hope)
- **Increase educational, research and training opportunities for a diverse pool of higher education students**
  - Community College Biophotonics Technician specialization (TVI)
  - Summer research program with extensive exposure to research and other professional possibilities + exchanges with MSI institutions
  - Biophotonics courses: Freshman introductory, advanced undergraduate and graduate
  - Human Development course to test and perfect K-5 after-school activities
  - Biophotonics track (undergrad) and designated emphasis (grad) at UCD
- **Engage the public in understanding the field of Biophotonics**
  - Public Events and talks at science centers
  - Public Friendly informative website (under construction)
- **Develop online resource for educators**

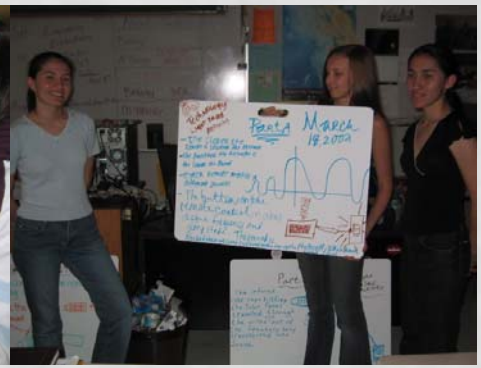



CBST Education - Intensive HS Research and Technology Training Program Highlights

Systematically Improve Science Education

- **WHAT:** Intensive 1 year program paid 200 hour program for 16 under-represented students. Focuses on the process of research and utilizing information technology while engaging in Biophotonics research. Year-long experience leads to a summer internship in a laboratory or other educational setting.
- **WHY:**Expose students to an emerging field while engaging them in learning information technology and research methodologies.
- **HOW:** in Collaboration with LHS (UC Berkeley) we are co-developing the curriculum with CBST focusing on Biophotonics research and LHS focusing on environmental research.
- **WHO:** We work with teachers that serve diverse student populations in Sacramento - Center HS and St. Hope - to help us develop the materials and recruit the students. Through the MESA network we can test prototype activities.



CBST Education - Higher Education Highlights

Systematically Improve Science Education

- **Community College Biophotonics Technician specialization (TVI)** - Undergoing course development with first trial Fall 2005
- **Summer research program** - 20+ students, over 40% under-represented, placed at various institutions including MSI partners
- **Biophotonics courses** - Multiple offerings at undergraduate level (UCD, UTSA, AA&M) and at graduate level.
- **Human Development course to test and perfect K-5 after-school activities** - great success in piloting activities and revising. Test programs with local Hispanic serving institutions.
- **UCD PhD students can now have "Biophotonics emphasis" on their diplomas - working on similar for undergraduates.**

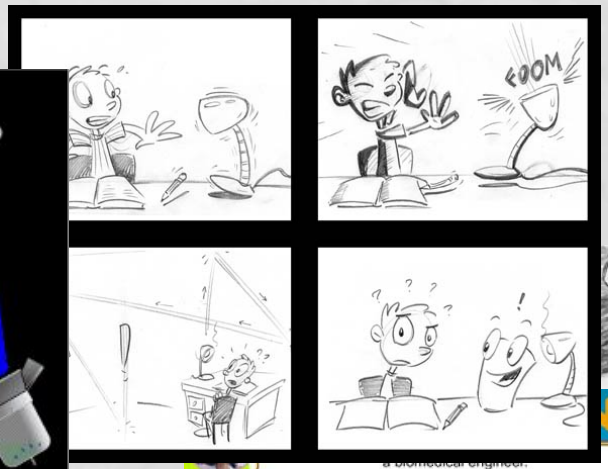


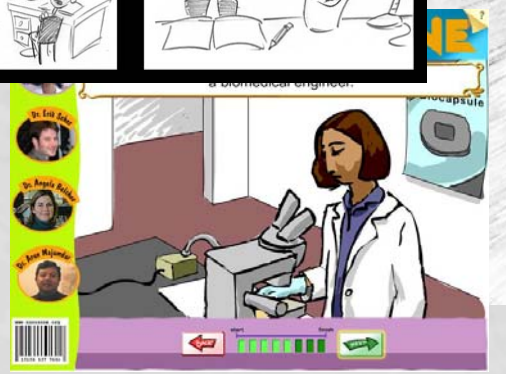


CBST Education - Resources and Public Highlights

Systematically Improve Science Education

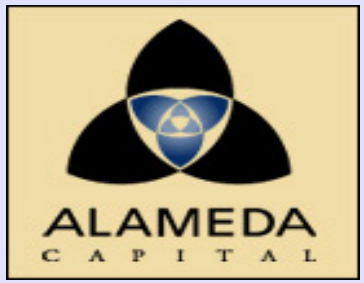
- **Educators website -** under development and will include our materials, exemplary simulations and Biophotonics information.
- **Public Venues with demonstrations -** UCD Picnic Day, Future Faire, Explorit science center lectures all continue and are being expanded.
- **Cartoons -** proposals have been submitted and are undergoing changes.
- **Research Kiosks -** proposals are being written.



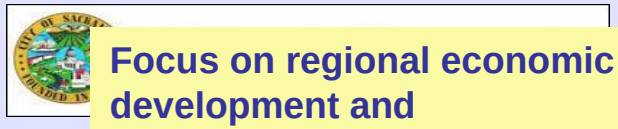


The CBST has multiple partners that encompass ALL areas of the Center's functions: Science & Technology, Education, & Knowledge Transfer

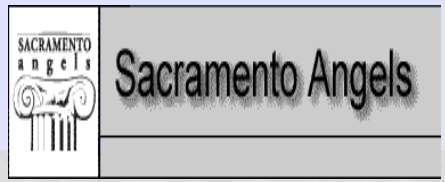
Technology Ventures Corporation



REGENT DEVELOPMENT PARTNERS



Focus on regional economic development and entrepreneurial opportunities for students/faculty



people

KNOWLEDGE TRANSFER
Knowledge Transfer ● Society Collaborations ● Public Relations

LEGACIES

People

- WORK FORCE CREATION: (Jobs)
  - Re-trained work force for regional growth of Biophotonics market sector
  - Created industry (professional) sanctioned class for professionals in Biophotonics

Tools

- KNOWLEDGE SOURCE: (Intellectual Capital)
  - Constructed a well-known and highly respected Biophotonics web portal with On-Line collaboratory
  - Built a “pipeline” for interactions with and communication among all participating institutions

Ideas

- COMMERCIAL & ECONOMIC DEVELOPMENT: (Business)
  - Established small businesses generate sales and stimulating regional economic growth
  - Developed new products launched and in clinical trials

CBST
CENTER for BIOPHOTONICS SCIENCE and TECHNOLOGY

KNOWLEDGE TRANSFER

Knowledge Transfer ● Society Collaborations ● Public Relations

CBST is creating a new Bio Zone by Uniting Academia & Industry

Cbst biozone

CBST
CENTER for BIOPHOTONICS SCIENCE and TECHNOLOGY

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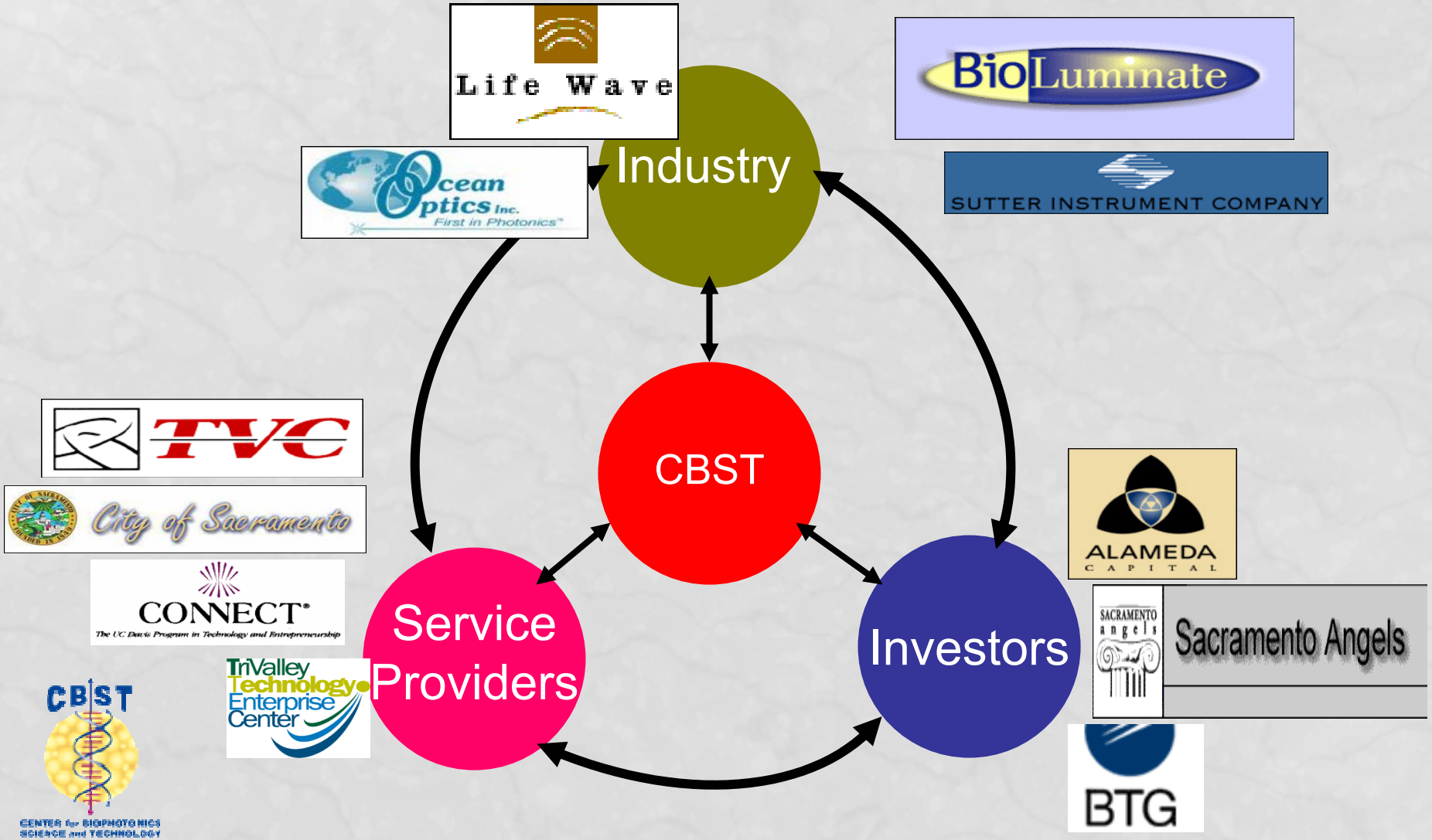
Catalyzing a Market Sector



CBST Enterprise HQ

- Physical laboratory facilities and infrastructure
  - Significant dedicated facilities at UCD Campus and UCDMC provided by UCD
  - Shared facilities for CBST activities at UCD, LLNL, UCSF, UCB, Stanford, Mills, other partners

National Science Foundation Center For Biophotonics at UC Davis
(Entrance)

2700 Stockton Blvd, Sacramento
17,000 sq. ft. laboratory, office, meeting space

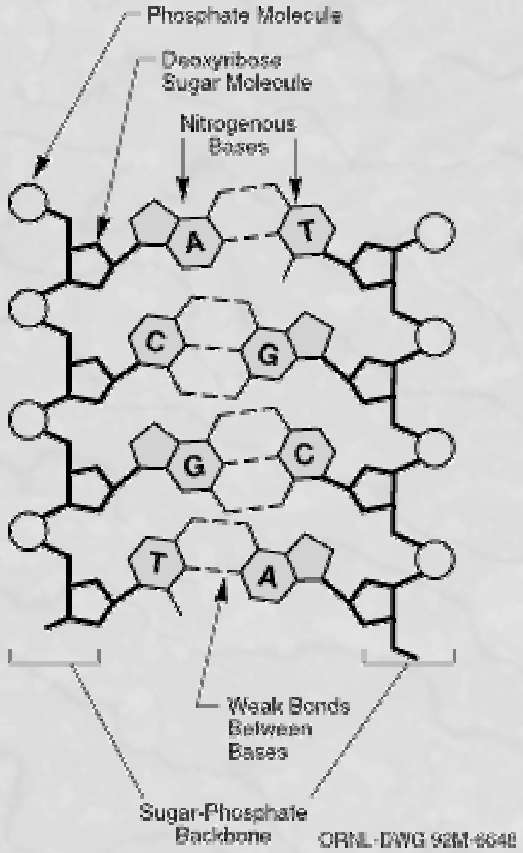
The Value of Interdisciplinary Teams

James Watson

Ornithologist
Virologist

Francis Crick

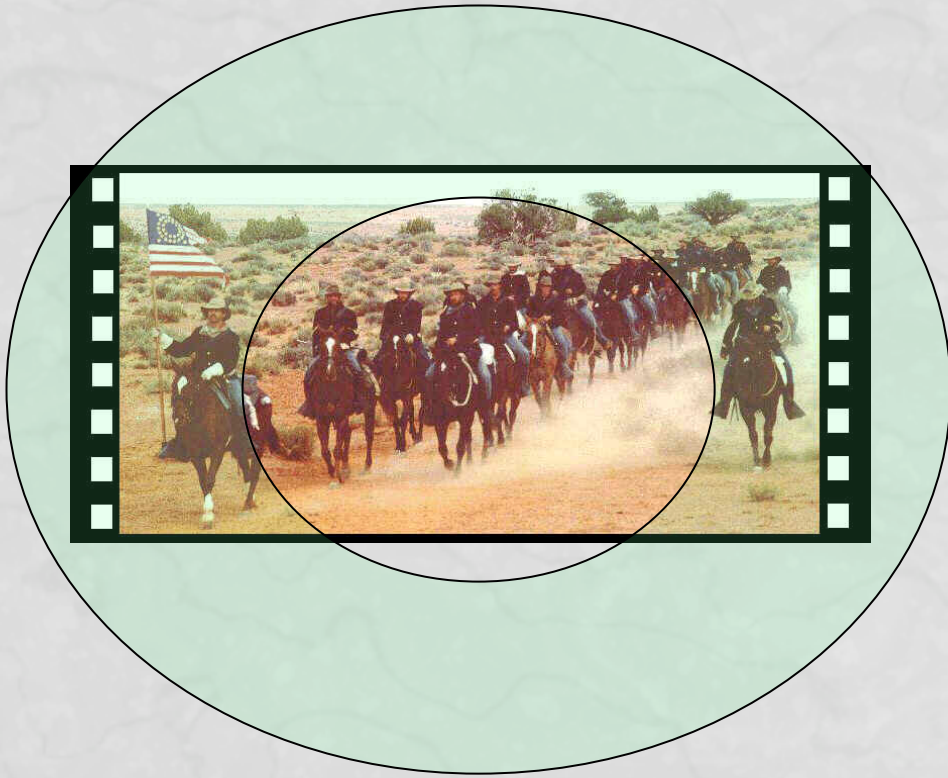
Physicist, Chemist
Biologist



DNA

Team Science

- **What is it? - Thematic or goal-driven R&D based on the directed contributions and collective reasoning and discovery of a multi-disciplinary group of individuals.. (this is not Webster's definition).**
- **For the official word on this see results of Becon 2003: http://www.becon.nih.gov/symposium2003**
- **My opinions --**
  - **Team Science is required for tackling grand challenges – hit rate too low with the lone hero approach**
  - **Everyone rewards the science hero, not a Team – ironic given our fixation with team sports**
    - **Industry & Fed labs foster teams**
    - **Academia and funding agencies have not historically**
  - **This is my job as a STC Director**
    - **To create a symphony out of virtuosos and prima donnas (and also with the "cards" I'm dealt!)**
    - **To help define and keep focus on goals and themes, derive consensus, create excitement/enthusiasm/momentum**
    - **To foster team sciene in the med/bio domain**
      - -MDs discover problems/needs and want to help solve
      - -Bioscientists define and help solve
      - -Physical Scienttists/engineers solve problems once discovered and defined
      - - MDs/Industry implement the new solutions



How do we foster collaborations among clinicians, physical scientists and engineers?

- **Brainstorming workshops, problem dissemination via web/email/telephone/whatever, breakout groups, proposal writing events, steering committee mtgs.. Involving Clinicians/Phys Scientists/Bioscientists in Center Leadership**
- **Recent example: Workshop with 100 clinicians/scientists/: "Application of Biosecurity Technology to Cancer" Breakout groups fueled team competitive spirit. Groups were forced to be interdisciplinary**

Charge to Participants

- **Learn about needs of Cancer researchers and clinicians**
- **Learn about key technologies and expertise in Counter Bioterrorism Program**
- **Create list of key medical needs vs. available or developable technologies**
- **Create list of hot topics for proposals**
- **Form teams to generate proposals to NIH**
- **Develop strategy for pursuing research projects that leads to seminal publications and scientific presentations**
- **Create means to pursue development of technologies into research or clinical devices**

Results - 5 theme areas and corresponding teams formed, ~30 proposal concepts suggested in one day, written proceedings generated.. - all in one day!

What are some of the barriers to collaborations

- Time (will make if project merits)
- Clinical Workload (Academic Physicians Must be Given Time for Research, Grants can help buy out of clinic if enough backup)
- Physical Separation (televideo, webcasting, collaboration portals…)
- Working day mismatch – bio/physical/engineers work weekdays, Docs do research on nites and weekends
- Lack of knowledge of field of medicine, physical or bioscience, bioengineering (don't be bashful)
- Lack of a Leader, Facilitator (very critical and among the hardest to arrange)
- Seed Funds to bridge to a new project
- …

The Center for Biophotonics Science & Technology

The Center for Biophotonics Science & Technology

UC Davis: Ron Baskin, Scot Simon, Yin Yeh, Jack Rutledge, Jim Boggan, Leslie Sandberg, Susan Autry-Conwell, Marco Molinaro, Jim Shackelford, Rich Ponzio, Clark Lagarias, Atul Parikh, Ann Orel, Nils Jensen, Dan Cox, Karen Reiser, Tom Jue, Xiangdong Zhu, Larry Morse, Rajiv Singh, Alexei Stuchebrukov……..

LLNL: Steve Lane, Rod Balhorn, Tom Huser, Rich London, Chad Talley, Chris Hollars, Chance Carter, Duncan Maitland, Mary McBride, Henry Chapman, Nan Shen, Stavros Demos, Tom Wilson, Jim Dunn, Pat Ambrose, Franz Weber,….

Mills: Susan Spiller……

UCSF: David Agard, John Sedat, Mats Gustaffson…..

UCB: Jay Groves….

Stanford: Chris Contag, Rajeesh Shinde, …

UTSA: Dhiraj Sardar, Randy Glickman …

AAMU: Ravi Lal, Anup Sharma, ….

Fisk: Arnold Burger, Marvin Wu,…

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