NISTIR 7305

Trends and Opportunities in Photonics Technologies: Solid-State Lighting and Healthcare

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June 2006

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I. INTRODUCTION

Photonics, the use of photons in optics, laser technology, electrical engineering, materials science, or information storage and processing[a], has migrated from being almost exclusively associated with research laboratories into mainstream industrial and consumer markets across the economy, including information technology, healthcare, security and safety, and lighting. In this document, we consider emerging photonic applications in the areas of solid-state lighting (frequently referred to as SSL) and medical applications. Our purpose is to provide a snapshot of the current state of photonics, as applied to SSL and healthcare, as well as to provide an estimate of future directions and anticipated achievements in these fields in the five to ten year time frame. At the same time, we will endeavor to highlight major technical barriers, as currently perceived, to reaching those goal. We base this document on a variety of sources of information. As detailed in Appendices I and II, we have interviewed NIST staff, both in the ATP and in the laboratories, representatives of other government agencies, and representatives from a variety of private companies. In addition, we have consulted reports and roadmaps generated by industrial consortia and government funding agencies.

Because the issues in SSL and healthcare are quite different, the two topics will be considered in separate sections. However, the format for the sections will be the same:

1) a description of the current status, including a synopsis of both the technology and the current applications,
2) a discussion of where the technology and applications are expected to be moving in the 1 to 10 year time frame, and
3) the technical/scientific barriers that need to be overcome for anticipated progress to occur.

It is our intention that this document provides insight both for the ATP to identify technical areas for expanded outreach activities and for the NIST laboratories to identify potentially high-impact areas for future research. To assist with this goal, we have included, in Appendix III a list of current and past ATP-funded projects in the areas of SSL and photonics in healthcare.

It should also be recognized from the outset that, because of regulatory considerations, the business models for healthcare applications are necessarily quite different from those for SSL. With SSL, an analysis of scientific barriers, device effectiveness, and cost comparisons provides a reasonable predictor of market penetration and economic benefits for specific applications. However, because safety concerns override economic benefit, healthcare applications, i.e., drugs, treatments, or devices, must undergo an additional level of scrutiny. This scrutiny is typically applied through clinical trials, which are both

[a] The American Heritage® Dictionary of the English Language, Fourth Edition Copyright © 2000 by Houghton Mifflin Company. Published by Houghton Mifflin Company.

expensive and time consuming. Because of the expense of the clinical trials, companies sometimes view certain products, which might prove highly competitive in niche markets, as not worth pursuing. In addition, unsuccessful or partially successful results of clinical trials can either terminate or greatly alter potential market applications in all healthcare products. The applications of photonics in healthcare discussed in this document are almost all in the pre-clinical testing stage. Therefore, while we discuss market and economic predictions due to advances in SSL, with regard to healthcare, we restrict our discussions to potential applications and do not attempt to predict market impacts.

II. SOLID-STATE LIGHTING (SSL)

Solid-state lighting is the name given to lighting generated through exciton recombination rather than through black body radiation (standard incandescent or halogen) or gas discharge (fluorescent or High Intensity Discharge). The basis of solid-state light emitting devices consists of an electron-rich (or easily injected) region and a hole-rich (or easily injected) region separated by a carrier depleted zone. When a voltage is applied electrons and holes are injected into the depleted region where they recombine, emitting light. This rather broad brush description is applicable to both light emitting diode (LED) based lamps, which are composed of traditional semiconductor materials, and organic light emitting diodes (OLED's), which are made of conduction and emission organic layers.

A. Current Status

The primary driving force for the development of solid-state lighting is the reduction of energy use, with concomitant reductions in chemical pollution, light pollution, and cost to the consumer. According to a 2003 report[1] by the Next Generation Lighting Industry Alliance (NGLIA), **in 2001, 22% of the electricity generated in the United States was used for lighting**. This is the equivalent output of 100 power plants, each generating 1000 MW, for a total cost of 55 billion dollars. The lighting requirements for 2005 in the United States are shown in Table 1[2], broken down into residential, commercial, industrial, and outdoor categories and into low, medium, high, and very high color rendering index (CRI)[b] bins.

Table 1: Sector and CRI estimates of teralumen-hours lighting demand in 2005 (after Reference 2)

(Tlm-h/y)	Residential	Commercial	Industrial	Outdoor	CRI-Bin Total
Low CRI	33	1,021	711	4,145	5,910
Medium CRI	1,336	12,451	3755	572	18,113
High CRI	62	7,932	4,258	64	12,316
Very High CRI	2,632	1,956	41	88	4,717
Totals	4,062	23,361	8,765	4,868	41,056

Table 1 shows that commercial lighting is expected to account for 74% of the generated light. For very high CRI, residential applications account for fully 55% of the usage.

According to the NGLIA report[1], when LEDs and OLEDs reach 150 lum/W for white light generation, the United States will be able to reduce its annual consumption of electricity by 6% - 7%, equivalent to about $17 billion. This reduction is projected to

[b] The CRI is a parameter that quantifies how closely the appearance of a set of eight pastel colors illuminated by a test lamp compares to the appearance when illuminated by an accepted "standard" lamp of the same light temperature (i.e., warmth). The maximum value of the CRI is 100, which corresponds to an appearance identical to that obtained from the reference lamp.

result in reductions of pollutants on the order of 150 x 10^6 tons of CO_2, 0.3 x 10^6 tons of NO_x, and 0.67 x 10^6 tons of SO_2. However, the current status of SSL sources falls well short of the 150 lum/W goal (in 2004, white LEDs lamps achieved ≅ 30 lum/W). Table 2 shows efficacy values[3] for three LEDs and one OLED that span the visible spectral range in 1999.

For comparison, an unfiltered incandescent lamp[2] has an efficacy of 10 – 25 lum/W and fluorescent lamps[2] reach 50 - 95 lum/W, depending upon the specific lamp geometry and application. By 2005, commercial LEDs improved to 100 lum/W at 50% wall plug efficiency.[4] In addition, commercial solid-state white lamps that provide 60 lum are now available, although they only provide about 15 lum/W. At this time, the DOE "World Record" for white lamps[5] is 74 lum/W for a laboratory LED and 20 lum/W for a laboratory OLED. Clearly, substantial progress needs to occur before the 150 lum/W goal is achieved.

Table 2: Typical efficacies of LEDs/OLEDs in 1999 (after reference 3)

Material	Color	Efficacy
InGaN	Blue	>10 lum/W
InGaN	Green	>25 lum/W
OLED	Green	>25 lum/W
AlInGaP/GaP	Red/orange	>100 lum/W

Along with the primary benefit of energy conservation, a number of secondary benefits also accrue with SSL. Possibly the most important secondary benefit is reliability. Today, blue LEDs provide over 5,000 h of light and red LEDs can last well over 100,000 h. When failure occurs, it is seldom catastrophic, as for incandescent and fluorescent lamps; rather, LEDs typically fail via a gradual diminution of light output over time. The long lifetimes and the non-catastrophic failure processes explain why LEDs have already made substantial inroads replacing incandescent traffic signal lamps and have almost completely replaced all other lamps for use in emergency exit signs throughout the United States.[6] In another aspect of reliability, the absence of breakable filaments contributes to make the idea of SSL attractive as light sources in environments inherently subject to vibration; e.g., instrument control lamps in all forms of transportation, overhead reading lamps in aircraft, brake lamps in automobiles and trucks, and vanity and door panel lamps in automobiles.

In addition to these prosaic, albeit important, benefits, SSL opens the possibility that architects, designers, and casual users of lighting will easily be able to achieve or to modify lighting-induced ambience without having to resort to energy robbing filters or having to maintain a collection of expensive specialty lamps. These possibilities include, but are not limited to, varying lamp color by mixing relative intensities of different colored LEDs or OLEDs, of dimming lamps without altering their color output, and, for OLEDs, of designing entire walls, table tops, or any other continuous surface to act as a controllable, distributed light source.[7] Finally, there are many niche markets that, while

forming only a small part of the overall lighting energy budget, would still provide substantial energy savings if incandescent lamps were replaced by SSL; the most important of these niche applications are holiday lighting and commercial signage.[6]

However, for SSL to displace most of these applications and, certainly, for it to disruptively take over any significant portion of the white light market, **three advances must occur: 1) the price must come down (for white LEDs, a reduction of x100 is needed), 2) the efficiency must increase, and 3) the reliability must increase** (this is especially important for OLEDs although it is also true for blue, green, and yellow LEDs). Because white-light lamps and area lighting form the largest component of the lighting budget and because efficient, reliable, and cheap generation of such white light from LEDs and OLEDs, which are inherently narrow in spectral output, forms the greatest barrier to the displacement of incandescent and fluorescent lamps by SSL, the remaining discussion of SSL will focus primarily on white lamps.

B. White Light Generation

There currently are three mechanisms by which solid-state lamps can produce white light:[3]

1) use of a blue source surrounded by a matrix containing one or two kinds of fluorescing particles, i.e., particles that will fluoresce in one or two wavelengths,
2) use of an UV LED surrounded by a matrix containing several different types of fluorescing particles, and
3) use of multiple active sources, either LEDs or OLEDs, to generate white light (Figure 1). This third approach avoids the need for fluorescent particles.

While it is commonly felt that the third approach will be the most efficient and is the most versatile, the first two approaches are more likely to enter the marketplace first.[3] Advantages and disadvantages with each approach are enumerated below.

1. Blue light source with phosphor particles

This approach uses a blue source that is surrounded by a matrix containing a single, yellow-fluorescing particle or a matrix containing two different fluorescing particles, e.g., a red and a green. The phosphor material can be a traditional fluorescent, similar in behavior although quite different in material requirements to coatings in fluorescent lamps, or the material could be made up of quantum dots (QDs). In either case, the lamp concept is the same. Because the phosphor particles only partially occlude the blue light source and because the capture and conversion efficiency of blue light by the fluorescing particles is less than 100%, the light out of the lamp is a combination of the fluorescing wavelength(s) and the original bluesource wavelength. By choosing phosphor particle wavelengths appropriately, the combination of fluorescence and blue source light results in a white output. Two of the main difficulties with this approach are the “halo” effect

and weak blue light absorption. The halo effect arises because the light from the blue diode is directional while the light from the phosphors is uniformly distributed. Consequently, while the center of the light spot appears white, the edges are dominated by the phosphor emission. Weak blue absorption requires thick phosphor layers. Currently, research is underway to make the diodes less directional in their output and to develop phosphor materials that are more efficient in both photon capture and photon emission.

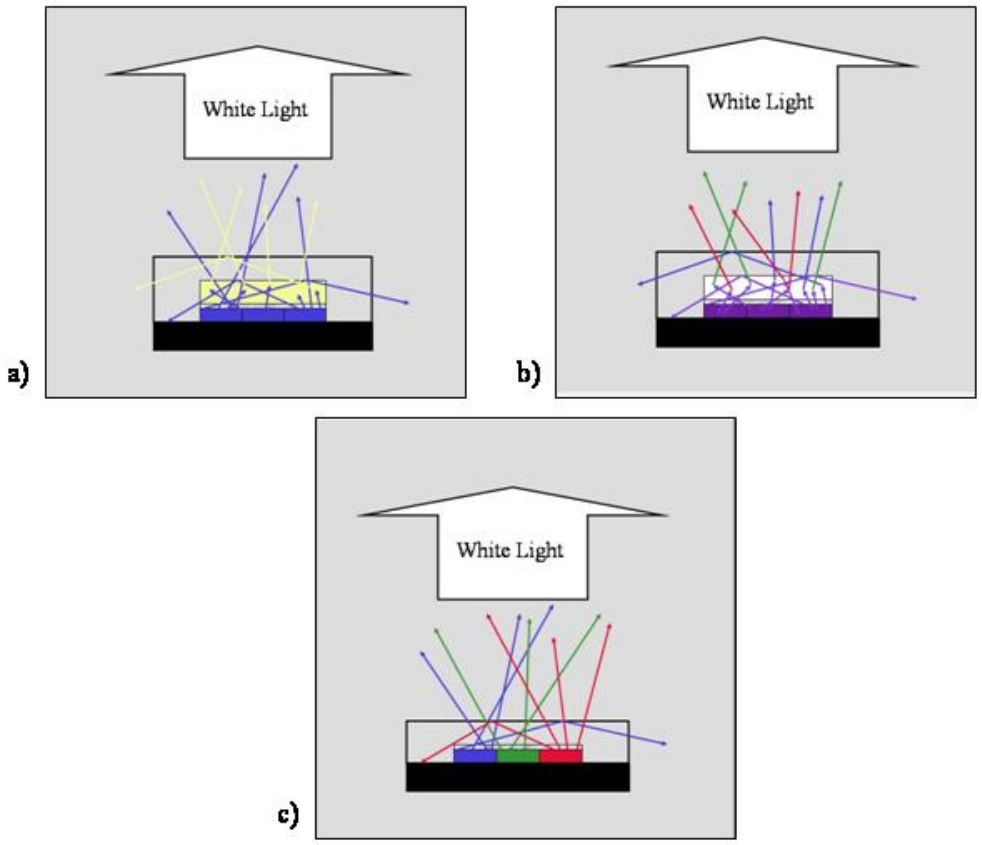

Figure 1: Schematics of the three approaches to making a white lamp. All three approaches involve placing LEDs or OLEDs (colored rectangles) on a conductor and substrate (shown schematically as the black rectangle). A transparent electrode is placed over the diodes and the entire system is enclosed in a hermetic seal that often acts as a lens. Differences in the approaches: a) A blue emitting LED excites a phosphor containing layer that emits complementary color(s), e.g., yellow. The combination of blue and phosphor generated colors gives a white light. b) An UV emitting diode excites a phosphor containing 3 colors whose combination gives a white light. c) Three distinct diodes emit red, green, and blue to give a white light.

2. UV LED with fluorescing particles

This approach is similar to the blue light source approach except that the LED output does not contribute to the visible light output. Therefore, all of the wavelengths required for white light generation must be supplied by the phosphors (i.e., phosphors for blue

output must be included into the layer). The UV excitation results in high CRI values but it also means that the phosphor particle, in addition to being thermally stable, must be stable under UV radiation. Additionally, because the LED is not contributing to the visible output, the phosphor particles must be highly efficient in converting the UV light. Finally, because UV radiation typically degrades polymers, this approach is more likely to be used for LEDs than OLEDs.

3. Three Color LEDs/OLEDs

Use of three independent colored LEDs to generate a white light has two important advantages. First, by avoiding the need for phosphor particles, the conversion efficiency of the phosphors no longer limits the efficiency of the lamps. Second, because the light is being generated directly from the LEDs/OLEDs, the output color can be controlled by individual control of the separate LEDs or OLEDs, i.e., intelligent pixel management. However, this control can be difficult, as pointed out in a report from the Optoelectronic Industry Development Association[3]: while "[i]n the long term, this option may be the preferred method for producing high quality white light for general illumination," these benefits come at a cost. "… [B]ecause the … different color components have different voltage requirements, different degradation characteristics and different temperature dependencies, a sophisticated control system might be required."[3] In addition, the lifetime of the lamp will be determined by the minimum lifetime of the various LEDs/OLEDs that contribute to the white light. Currently the lifetime of red LEDs is 5 times that of blue LEDs. To achieve the desired lamp lifetimes, degradation mechanisms for the blue, green, and yellow sources must be identified and solutions to the degradation must be developed. Finally, there currently are no efficient green LED candidates. Therefore, for solid-state white lamps, without phosphor particles, there is an urgent need for the development of green LEDs to achieve the correct color control.

C. Scientific and Technical Barriers

The process of generating white light from solid-state sources requires several steps, each of which involves its own loss mechanisms and concomitant cost in efficiency. Because the overall device efficiency is the product of these individual efficiencies, each step in the process must be optimized to maximize the overall efficiency of the final device. A simplistic description of the key processes involved in developing a white lamp will help clarify the research and development prioritization schemes that are discussed below. In SSL, photons are generated via recombination of electrons and holes. Mechanisms that reduce carrier concentration, carrier mobility, or non-radiative exciton recombination limit the net output of the device. Therefore, such things as electric fields that inhibit charge injection, Fermi surfaces that reduce mobility, and point/distributed defects that act as alternative trapping sites, need to be identified and reduced or eliminated in order to increase light generation. Once generated, photons must escape the material without being reabsorbed or scattered into non-productive pathways. Consequently, the active region needs to be thin, the index of refraction for the surrounding material needs to be large and the geometry of the active region needs to be designed to minimize internal reflection. If the white lamp depends on down-conversion of blue or UV light, the

efficiencies of the phosphor particles in capturing the excitation photons and in converting the energy of the captured photons into light act as additional limiting factors on the overall efficiency of the lamp. Additionally, for down-conversion lamps, the phosphor particles and their surrounding matrix must withstand high intensities of blue or UV light with minimal property degradation in order for the lamp to achieve the desired lifetime of multiple tens of thousands of hours. Finally, thermal management of the lamp is essential at all scales. While SSL generates light by direct electron/hole recombination rather than by joule heating, as an incandescent lamp does, the fact remains that, if a lamp has a 50% wall plug efficiency, as the best commercial LEDs currently do, then half of the energy used by the lamp will be converted to heat. If SSL is improved to achieve the goal of 80% wall plug efficiency, there will still be 20% of the energy being used to generate heat within the lamp. While much less energy is being used to generate heat in SSL than in incandescent lamps, the heat is being generated in very small volumes and can result in locally large thermal excursions that lower the efficiency, alter the output wavelengths, and degrade the lifetimes of the lamps. Therefore, thermal management is a critical aspect of SSL design from the semiconductor size scale all the way through the lamp and housing scale. These various issues form the basic conceptual barriers that must be addressed for SSL to function. However, for SSL to succeed as an industry, the solutions to these barriers must be economical and practical as well as scientifically possible.

At the spring Department of Energy (DOE) SSL Workshop and Program Review[8] held in San Diego, CA, February 3-4, 2005, industry, national lab, and university representatives discussed the scientific and technical barriers that must be overcome for SSL to displace incandescent and fluorescent lighting. The identified barriers were prioritized in terms of urgency and, based upon that prioritization, were placed into 2 – 3 year or 5 – 10 year time-frame bins. Because the barriers are essentially the same as those previously identified by the Optoelectronic Industry Development Association (OIDA),[3] the NGLIA,[1] National Electrical Manufacturers Association (NEMA),[9] and a presentation made by a SSL company, LUMILEDS, at a DOE conference on SSL,[10] the discussion of technical barriers and priorities below will focus predominately on the consensus-based conclusions reached at the February 2005 DOE Program Review.

Figure 1 lays out the primary barriers that must be overcome for SSL to break into the lighting industry at a substantive level. The figure is divided into issues associated with inorganic SSL, or LEDs (Fig. 1a), and those associated with organic SSL, or OLEDs (Fig. 1b). Issues are divided into needed progress for both LEDs and OLEDs:

- further research and understanding are necessary (Core Technology)
- basic understanding is (or will be) in place and the remaining barriers are engineering and economic (Product Development).

Items that are italicized were, by consensus of the participants, determined to be the most urgent items; i.e., issues that need to be addressed in the 1 – 3 year time frame. The remaining items need to be addressed in the 5 – 10 year time frame or, in a few cases, are expected to be issues that would be addressed by individual companies on a proprietary

Issues Associated with Inorganic Solid State Lamps

- **INORGANIC SSL "CORE TECHNOLOGY" RESEARCH**
- **Inorganic Materials Research**
  - *Large area substrates, buffer layers, and wafer research*
  - *High-efficiency semiconductor materials*
  - Reliability and defect physics for improved emitter lifetime and efficiency
- **Inorganic Device Architecture Research and Modeling**
  - *Device approaches, structures and systems*
  - *Strategies for improved light extraction and manipulation*
- **Inorganic Integration Technology Research**
  - *High-efficiency phosphors and conversion materials*
  - Encapsulants and packaging materials
  - Electrodes and interconnects
  - Measurement metrics and human factors
- **Inorganic Growth and Fabrication Processes and Manufacturing Research Issues**
  - Physical, chemical, optical modeling measurement, and experimentation for substrate and epitaxial processes
  - Design and development of in situ diagnostic tools for substrate and epitaxial process
  - Research into low-cost, high-efficiency reactor designs and manufacturing methods
  - Investigation (theoretical and experimental) of die separation, chip shaping, and wafer bonding techniques

- **INORGANIC SSL "PRODUCT DEVELOPMENT"**
- **Inorganic Materials and Device Architecture**
  - Substrate, buffer layer and wafer engineering and development
  - High-efficiency semiconductor materials
  - Implementing strategies for improved light extraction and manipulation
  - Device architectures with high power-conversion efficiencies
- **LED Component Technical Integration**
  - *Manufactured materials*
  - *LED packages and packaging materials*
  - Modeling, distribution, and coupling issues
  - Evaluate component lifetime and performance characteristics
- **System Technology Integration and Novel Luminaire Design**
  - *Optical coupling and modeling*
  - Mechanical design
  - *Electronics development*
  - *Thermal design*
  - Evaluate human factors and metrics
  - Evaluate systems lifetime and performance characteristics
- **Inorganic Growth and Fabrication Processes and Manufacturing Issues**
  - Incorporate proven in situ diagnostic tools into existing equipment
  - Develop low-cost , high-efficiency reactor designs
  - Develop techniques for die separation, chip shaping, and wafer bonding

Figure 1a: Scientific/technical and developmental barriers that must be overcome for LEDs to take over substantial portions of the white lamp market (after Reference 8). Italicized items are deemed most urgent, i.e., 1 – 3 year time frame. Remaining elements fall into the 5 – 10 year time frame.

Issues Associated with Organic Solid State Lamps

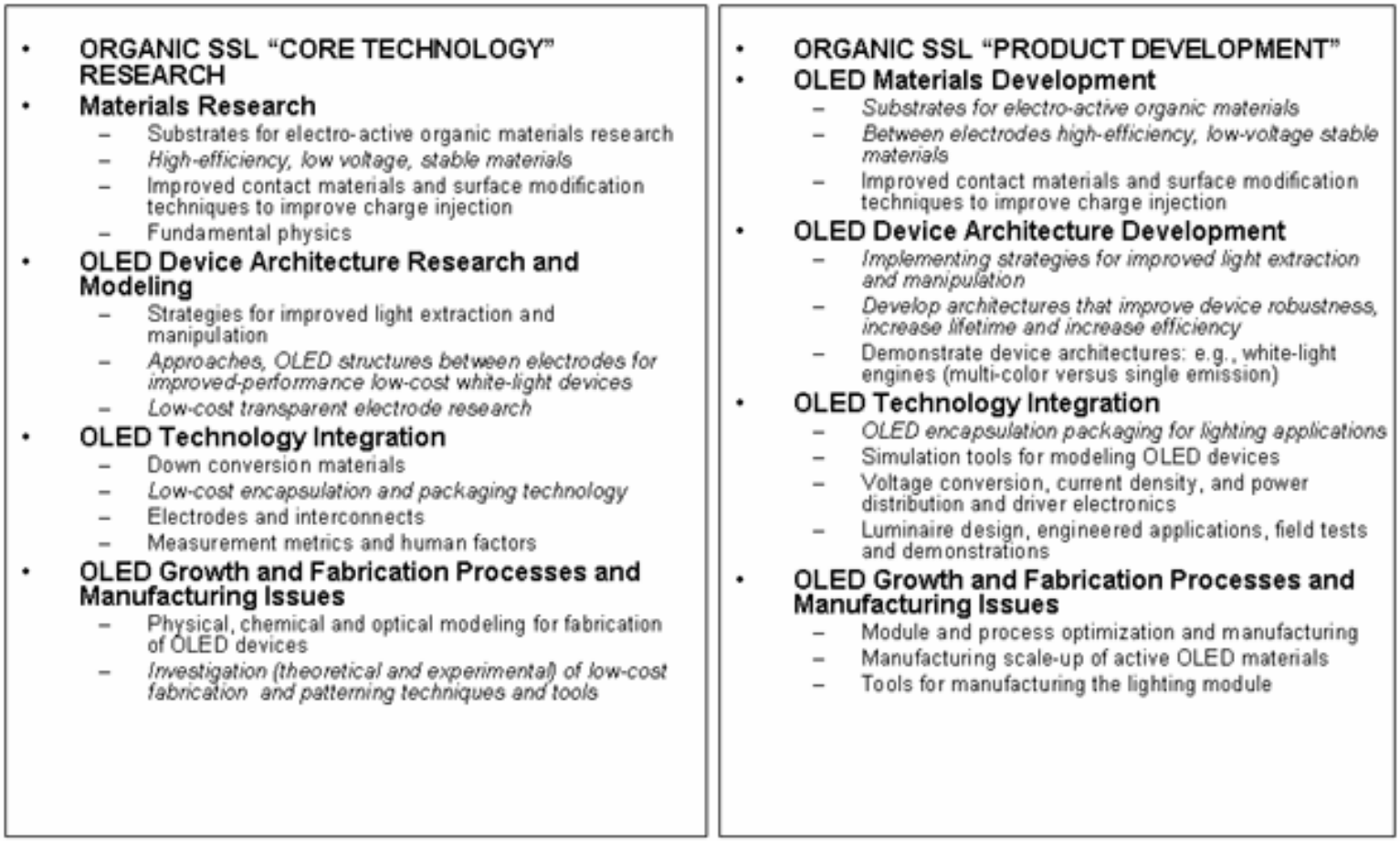

Figure 1b: Scientific/technical and developmental barriers that must be overcome for OLEDs to take over substantial portions of the white lamp market (after Reference 8). Italicized items are deemed most urgent, i.e., 1 – 3 year time frame. Remaining elements fall into the 5 – 10 year time frame.

level rather than on a consortium level. The following discussion addresses topics in both the 1 – 3 year time frame and the 5 – 10 year time frame. The ordering presented in the 1 – 3 year time frame discussion has no significance; the five items at the workshop that received the largest number of votes in each category were designated as the most urgent. The number of attendees at the workshop was not large enough to allow a meaningful prioritization of the five "most urgent" items in each category.

1. 1 – 3 year

a) Inorganic Core Research

In this area, the five most urgent research areas are: 1) large area substrates, buffer layers, and wafer research; 2) high-efficiency semiconductor materials; 3) device architecture approaches, structures, and systems; 4) strategies for improved light extraction and manipulation; and 5) phosphors and conversion materials. Some of the key aspects of each of these areas are:

1) Large area substrates, buffer layers, and wafer research
    a. Defects in substrates that propagate into the film active areas act as non-radiative recombination sites that degrade the efficiency of the light-emitting devices built on the substrates. Therefore, defect reduction in substrates is a high priority. However, defect reduction becomes increasingly difficult as substrates with larger areas are grown.
    b. Ideal buffer layers between the substrates and the actives layers will not only isolate the active layers from defect propagation from the substrate but will also reduce dislocation formation in the active layers that results from thermal expansion mismatch between the substrate and subsequent film layers. The buffer layers need to accomplish this while allowing a high level of crystalline perfection in the active layer.
    c. Research into fabrication of high quality (i.e., low defect density) wafers that come close to lattice matching the active layers could result in much lower dislocation densities in the active layers and avoid the need for the buffer layers. The nitrides are prime contenders in this area. In addition, ZnO is being investigated as a material that provides an alternate path.
2) High-efficiency semiconductor materials
    a. As mentioned previously, one of the highest priorities for multicolor LED white lamp fabrication is the development of an efficient, long-lived green LED.
    b. In addition to development of an adequate green LED, cost reduction and reliability improvement of all of the nitride-based and ZnO-based LEDs remain high priority research areas. Increasing the active area, i.e., defect free region, of nitride films would provide an economy of scale as well as lead to more efficient LEDs.
3) Device architecture approaches, structures, and systems

    Directional light emission, either through light generation via directed sources, e.g., lasers, or through post-generation guidance, e.g., photonic crystals, would help alleviate light extraction issues associated with internal

reflection. Directional sources would also be valuable in the development of SSL spot sources or accent lamps that would provide light where needed while reducing wasteful and undesirable light pollution. In addition, improved procedures such as surface preparation, e.g., roughening and faceting, or index matching to reduce internal scattering and improve extraction efficiency, fit within this task definition.

4) Strategies for improved light extraction and manipulation
   This task has the same goal as task 3, above. However, the emphasis here is on modeling or highly innovative ideas that can be used to increase light extraction and directional control.
5) Phosphors and conversion materials
   a. Optimization of deposition methods, particle packing and distribution, particle layering, particle conversion efficiency, and matrix optical properties are critical to enhancing the efficiency of the down-conversion of the incident light. This task also includes issues such as design requirements to enhance forward scattering, rather than backscattering of the incident light and reduction of secondary absorption in the phosphorescing particles.
   b. In addition to control of initial optical properties and conversion efficiencies of the phosphorescent particles, SSL requires long-term stability. Therefore, degradation mechanisms, via exposure to high intensity incident light, high local thermal excursions, chemical interface interactions, etc., must be identified and quantified, and strategies for minimizing degradation must be developed.

b) Inorganic Product Development

The corresponding five most urgent items for inorganic LED "Product Development" are: 1) integration of manufactured materials, 2) integration of LED packages and packaging materials, 3) optical coupling and modeling, 4) integration of electronics design, and 5) integration of thermal design.

1) Integration of manufactured materials
   The integration of the phosphor particles with the encapsulate material and mounting materials must include optical, thermal and chemical compatibility of each of the individual materials as well as stability among the materials.
2) Integration of LED packages and packaging materials
   a. Integrated packages must include compatibility with both electrodes, and commercial design requirements as well as a thermal management system (i.e., thermal pathways to dissipate heat without interfering with optical requirements).
   b. Compatible electrodes must be chosen to fit package design requirements, e.g., transparent or opaque, low resistance, high adhesion.
3) Optical coupling and modeling
   Although each of the individual material optical properties was addressed under "Core Technology", the integration of the elements can lead to

unforeseen complications. In particular, optical paths and optical interfaces must be carefully modeled and designed to achieve high efficiency lamps.

4) Integration of electronics design

   As alluded to previously, the electronics for SSL must be designed to provide the required voltages and currents without occluding the optical pathways and while maintaining the desired form factor. The electronics must also be designed to minimize joule heating in the lamps. In the case of multi-LED lamps, the current and voltage requirements, and associated controllers, for each LED must be designed and then integrated into a single package.

5) Integration of thermal design

   Thermal issues have been mentioned several times previously and thermal management must be incorporated at each step in the lamp design. The integration of multiple materials and, potentially, multiple current and voltage sources into very small volumes make thermal management of the entire system complicated. Current high intensity white lamps incorporate large heat sinks that greatly increase the lamp size and mass. It is commonly assumed that future lamps will need to be designed to minimize such heat sinks, both for practical as well as aesthetic reasons.

It is important to bear in mind that, in the DOE SSL framework, the tasks listed under "Product Development" are expected to require minimal additional research. At this stage, the expectation is that the tasks should be headed toward commercialization. However, with regard to the NIST mission, the Product Development tasks remain important for two reasons. First, as commercialization is begun, issues associated with standards become more evident. Second, the steps between basic understanding, i.e., "Core Technology," and commercialization lie precisely in the mandated mission of the Advanced Technology Program. Therefore, knowledge of these issues could allow DOE and NIST/ATP to leverage off of each other's resources, to the benefit of all.

c) OLED Core Research

Exactly the same process was used to identify the five most urgent issues on "Core Research" for OLEDS:

1) High efficiency, low voltage materials;
2) Approaches, structures, and systems for improved-performance;
3) Transparent electrodes;
4) Low-cost encapsulation and packaging technology; and
5) Investigation of low-cost fabrication and patterning techniques.

d) OLED Product Development

1) Substrates for electro-active organic materials.
2) High efficiency, low voltage, stable materials.
3) Implementing strategies for improved light extraction and manipulation.
4) Develop architectures that improve device robustness, increase lifetime and increase efficiency.
5) OLED packaging for lighting applications.

It is immediately clear that many of the issues associated with LEDs and OLEDs are the same, albeit, because of the differences between material properties of semiconductors and polymers, typically different solutions to technical barriers will be required. Nevertheless, efficiency, improved device structure, improved light extraction, low cost packaging technology, increased lifetimes, and thermal management are critical areas that need to be addressed in both materials systems. Indeed, one of the suggestions that came out of the workshop[8] is that there needs to be "more cross-fertilization between LED and OLED" activities. However, because of the inherent differences in long-term stability between semiconductors and polymers, there is substantially greater emphasis in the OLEDs on low voltage materials, improved performance, and improved lifetimes.

2. 5 – 10 year time frame

Longer-term research and development requirements exist. Some of the items are considered long term because they reflect ongoing improvements and extensions of the current state of understanding in the basic sciences that underpin SSL. Others tasks are considered long term because their implementation is predicated on solutions being found for the more urgent, 1 – 3 year tasks discussed above.

a) Inorganic Core Technology

High priority inorganic "Core Technology" research issues in the 5 – 10 year time frame are: 1) development of reliability predictions and defect physics for improved LED lifetime; 2) development of improved encapsulate and packaging materials; 3) development of improved electrodes and interconnects; 4) development of measurement metrics and human factors for SSL; 5) improved physical, chemical, and optical modeling for epitaxial processes; and 6) design and development of *in situ* diagnostic tools for epitaxial processes.

1) Development of reliability predictions and defect physics for improved LED lifetime.
    a. An improved theoretical understanding and associated experimental tools are desired for predicting material or device properties as well as device failure interpretation. Current models are more empirical and/or qualitative than desired for device design or lifetime prediction, particularly as materials used in SSL evolve.
    b. Droop, i.e., efficiency degradation at high temperature and current density, is a well recognized but poorly understood phenomenon. Accurate theoretical analysis with experimental confirmation is needed for droop to be overcome in current device designs and avoided in future devices.
2) Development of improved encapsulate and packaging materials.
    a. Similar to the phosphor particles and the active light generation medium that are highlighted in tasks for the 1 – 3 year time frame, packaging materials have to withstand elevated temperature, high intensity of visible and, perhaps, UV radiation, and environmental attack while allowing efficient optical extraction. In addition, the

packaging material has to maintain its properties for the lifetime of the lamp.

b. As discussed previously, thermal management is a ubiquitous and potentially limiting issue that must be addressed at every level of lamp design.

3) Development of improved electrodes and interconnects.

Low resistance electrodes and interconnects are important to reduce thermal loading and improve lamp efficiency. Additionally, issues such as adhesion reliability are poorly understood and potentially limit device lifetime.

4) Development of measurement metrics and human factors for SSL.

a. The interface with human usage and perception is critical for the widespread adoption of SSL. Human experience, expectations, and preferences for lighting need to be incorporated into lamp design; regardless of lamp efficiency and output power, if the lamp output is not perceived to be attractive, convenient, or desirable, SSL will not replace current lamps in the general lighting market.

b. Industry definitions of "white" light, and "quality" of light need to be developed and adopted. The variation of both white light and quality of light with specific applications need to be designed into lamps.

c. Standards for photometric measurements need to developed and adopted by the industry.

5) Improved physical, chemical, and optical modeling for epitaxial processes.

Improved theoretical understanding of epitaxial processes needs to be developed, both to provide better control of current material systems and to provide guidance for material systems of the future.

6) Design and development of in-situ diagnostic tools for epitaxial processes.

Tools need to be developed, in parallel with item 5) above, to provide real time, quantitative evaluation of film systems.

b) Inorganic Product Development

The 5 – 10 year time frame tasks for the inorganic SSL "Product Development" are closely tied to success of the 1 – 3 year tasks of the inorganic "Core Research". In particular, four tasks in Materials Development are clearly dependent upon success in development of large, low defect density substrates, improved buffer layers, new high-efficiency LEDs that span the visible spectrum, and improved high-efficiency phosphors. These tasks are: 1) substrate, buffer layer, and wafer engineering and development; 2) high-efficiency semiconductor materials; 3) implementing strategies for improved light extraction and manipulation; and 4) device architectures with high power conversion efficiencies. Two other long-range goals, modeling of coupling issues for device integration and luminaire design and field tests, build upon the short-range tasks 1 and 2 (i.e., packaging issues) for inorganic "Product Development". The final two "Product Development" long-range activities, (a) evaluation of human factors and evaluation of lifetime and (b) performance characteristics, are tightly coupled to similar long term tasks laid out under "Core Research".

c) OLED Core Research

In the 5 – 10 year time frame, the following tasks exist for OLED "Core Research":

1) Research into electro-active organic materials for substrates.
    a. Addresses the difficulties associated with achieving efficient charge injection into the polymer semiconductors from the perspective of material development
2) Improved contact materials and surface modifications for improved charge injection.
    a. Addresses the difficulties associated with achieving efficient charge injection into the polymer semiconductors from the perspective of interface effects
    b. Replaces the insulating substrate and the conducting film that lies between the substrate and the semiconducting polymer with an electro-active polymer substrate that has a work function comparable to the HOMO level of the semiconductor.
    c. One consequence of low charge injection and mobility is the need for higher driving voltages (e.g., 10 – 20 volts instead of the desired 4 volts).
3) Improved understanding of the fundamental physics associated with OLEDs.
    a. The details of charge injection, mobility, and recombination need to be better understood for OLEDs.
4) Strategies for improved light extraction.
    a. This item is similar to the light extraction issues with LEDs discussed previously. Non-radiative recombination processes, scattering, and re-absorption need to be reduced to improve the efficacy of OLEDs.
5) Down-conversion materials.
    a. Again, the issues in down conversion are the same as the down conversion requirements in LEDs: quantum efficiency, long-term reliability.
6) Integration of electrodes and interconnects.
7) Measurement metrics and human factors.
    a. The issues associated with measurement metrics and human factors (e.g., color quality, color acceptability) are identical to those mentioned above for LEDs. The longer time frame for this item in OLEDs reflects the feeling that efficacy, reliability, voltage, etc. are a more urgent priority for OLEDs and that human factors will follow after more immediate problems are solved.
8) Improved physical, chemical, and optical modeling.
    a. It is generally felt that modeling tools are not well established for OLEDs. This reflects the general feeling that understanding of the basic physics in OLEDs is not yet adequate.

d) OLED Product Development**.**

In the same time frame, the OLEDs "Product Development" tasks are:

1) Improved contact materials for improved charge injection;
2) Demonstration of various device architectures;

3) Simulation tools for modeling OLED devices;
4) Voltage conversion, current density, power distribution and driver electronics;
5) Luminaire design and field tests;
6) Module and process optimization and manufacturing;
7) Manufacturing scale-up of OLED material; and
8) Tools for manufacturing lighting modules.

Issues associated with manufacturability are built closely upon the perceived Core Research needs discussed previously. In addition, a number of these tasks mirror similar tasks associated with the LED lamp fabrication. These include strategies for improved light extraction, improved down-conversion materials, integration of electrodes and interconnects, measurement metrics and human factors, improved physical, chemical, and optical modeling, demonstration of various device architectures, driver electronics, luminaire design and field tests, and tools for manufacturing lighting modules. However, other tasks are more specifically related to the polymer aspects of OLEDs. In particular, the issues associated with charge injection, electrically active substrates, and manufacturing scale-up in OLEDs are quite different from the same issues associated with LED lamps. Finally, it should be noted that, while modeling and theory development are highlighted as needs for both LEDs and OLEDs, improved understanding of the fundamental physics is most pressing for OLED development.

3. Additional considerations

In addition to obtaining information from DOE, OIDA (Optoelectronic Industry Development Association), and industry sponsored workshop summaries and reports, information was also obtained from numerous individuals within various private companies involved in SSL development. Conversations were explicitly restricted to nonproprietary topics, focusing on generic, industry wide issues that NIST might address, i.e., standard reference materials, standard measurement procedures, basic research advances. While most of the topics that arose have been covered above, there was a repeated emphasis on the thin film aspects of SSL that was not explicitly addressed in any of the workshops or reports that we have seen. In particular, concerns exist over appropriate measurement techniques and data interpretation for very thin film systems, e.g., whether material properties remain the same as films are reduced to tens of nm in thickness, and what might be the impacts of reducing size to the point that systems are dominated by surface and interface properties rather than by bulk volume properties. In particular, questions exist regarding the proper procedures for measuring and interpreting thermal conductivity in systems composed of layers of very thin films. How does thermal conductivity of a film behave as film thickness decreases? These are particularly important problems as device size continues to shrink; designs for thermal management in these complicated thin film systems are made using models that assume bulk material thermal properties. Similar concerns accrue to other material properties as film thicknesses continue to shrink; e.g., how do optical properties like index of refraction behave? Will delamination become a problem as thicknesses continue to decrease? What impact do the large surface/interface areas have on long term reliability? These

questions become increasingly difficult to answer as size scales in SSL devices move into the nanometer range.

D. NIST Interaction Opportunities in SSL

Several organizations exist in the United States that either are currently active in SSL or have been heavily involved in the recent past. These organizations include government agencies, industry consortia, individual companies, and universities. A list of key organizations whose output and conclusions have been used in this report is presented below. We also provide a short discussion of potential interaction benefits to both the NIST laboratories and the NIST ATP for each organization.

1. DOE

The Department of Energy (DOE) has become the national driver for SSL. This reflects three facts: 1) energy conservation is part of thr DOE mission, 2) as the head of a collection of national laboratories, the DOE has substantial research resources that it can direct towards SSL and 3) as the primary source of non-Department of Defense research funding in the United States, the DOE has financial resources to support industry efforts in both basic SSL research as well as in commercialization efforts. Two parts of the DOE are involved in the SSL program: the Office of Energy Efficiency and Renewable Energy (EERE)/Building Technologies and the National Energy Technology Lab (NETL). The overall program is directed by Dr. James Brodrick of the Office of Building Technologies.

a) NIST Laboratories

There are three benefits for the NIST laboratories in working with the DOE SSL program. First is the possibility for setting up collaborations with industry or DOE laboratory partners who are either currently receiving funding or are attempting to put together a research plan in order to receive future funding. Second is that the SSL program provides a prioritized list of research areas with clearly associated industry impacts that can help to guide NIST laboratories research choices. Third is the potential to leverage funding for LED or OLED material or device issues for both agencies. Priorities are re-evaluated yearly at the DOE program reviews, in light of yearly progress and potentially evolving priorities.

b) ATP

As discussed previously, the DOE SSL program is divided into two components: “Core Research” and “Technology Development”. Funding for Core Technology is intended to provide resources for overcoming scientific barriers to SSL. Funding for Technology Development is not intended for research; rather, it is intended for product development and commercialization. One feature of the DOE SSL program is that an industrial organization, the Next Generation Lighting Industry Alliance (NGLIA), provides technical guidance and has access to patented non-commercialized intellectual property (IP) that is developed under SSL Core Technology funding (see discussion below). An opportunity for the ATP is to provide funding to small companies that have patented IP

but have remaining high risk scientific/technological barriers to overcome prior to commercialization. These conditions precisely meet the ATP mandate.

2. National Electrical Manufacturers Association (NEMA)

NEMA "is the leading trade association in the U.S. representing the interests of electroindustry manufacturers of products used in the generation, transmission and distribution, control, and end-use of electricity."[9] As part of its activities, NEMA develops manufacturing roadmaps, develops standards, and lobbies for the interests of manufacturers in the electric and electronic industries. Recently, NEMA has expanded its activities to include SSL. As one of the activities associated with SSL, NEMA manages NGLIA, although NGLIA is not a part of NEMA.

a) NIST Laboratories

Many NIST staff members participate in NEMA road-mapping efforts and in standards activities involving NEMA. NIST management also has a history of involvement with NEMA, e.g., attending meetings and giving presentations. These activities provide guidance as to industrial directions, allow NIST staff to develop relationships with industrial counterparts, and enhance opportunities for the NIST/industry collaborations.

b) ATP

Outreach activities to NEMA, via road-mapping activities, standards work, or meeting attendance, would provide ATP staff with the same opportunities as the laboratory staff to develop personal relationships with industry members as well as, both formally and informally, educate industry counterparts regarding the existence and purpose of the ATP. In addition, participation of ATP staff in road-mapping and/or standards discussions enhances ATP stature as being technically aware, informed and active.

3. Next Generation Lighting Industry Alliance (NGLIA)

The NGLIA is an industry consortium focused on SSL under the DOE program. One of the benefits of being a member of the NGLIA is that any patented IP developed under the DOE SSL "Core Research" Program that is not in the process of being commercialized one year after the patent award is available to any consortium member under a non-exclusive license for "reasonable terms".[11] The consortium is managed by, though not a part of the National Engineering Manufacturing Association (NEMA). As of February, 2005, the consortium members are: Corning, Cree, Dow/Corning, General Electric, GELcore, Kodak, Lumileds, OSRAM, Philips, and 3M.

a) NIST Laboratories

The primary potential benefit to the NIST laboratories for interaction with NGLIA is that NGLIA research directions and goals are shared by the major companies involved in the SSL industry. This provides guidance to the laboratories regarding the potential economic impact associated with SSL research directions. In addition, because the NGLIA provides technical guidance to the DOE regarding SSL road mapping, NGLIA endorsement of the importance of a proposed NIST laboratory activity enhances the importance that the DOE will place on the proposal.

b) ATP
If the ATP is conducting outreach activities to NEMA and sets up a relationship with DOE that will allow presentations at the DOE SSL program reviews, an explicit outreach activity to NGLIA sponsored meetings may be repetitive. This is particularly true since most of the members of NGLIA are clearly aware of both the existence and purpose of ATP, having submitted proposals in the past.

4. Optoelectronic Industry Development Association (OIDA)
OIDA is an industry consortium made up of predominately U.S. companies involved in photonics. As recently as 2000, manufacturers making up 80% of the dollar value of photonics manufacturing and sales in the United States were members of the OIDA. Until the recent economic downturn, fiber optic communications, networking, and optical computing were the main thrusts of OIDA. Around 2001, the OIDA began promoting the importance of SSL and educating Congress regarding the relevant issues. Since that time, the DOE has become the champion for SSL and the OIDA has turned its focus toward optical sensors. Nevertheless, the OIDA has organized excellent workshops and published reviews of the issues associated with SSL that provide important and relevant information.

a) NIST Laboratories
The NIST laboratories have had a close working relationship with the OIDA for many years. This is particularly true for the Optoelectronics Division in the EEEL, which has based much of its choice of technical direction upon OIDA-generated roadmaps. However, because the OIDA represents such a large portion of the optoelectronics industry, CSTL, MSEL, and PL also have a track record of interacting with the organization, both in conducting research suggested by OIDA roadmaps and in participation at OIDA meetings. These roadmaps have provided and continue to provide valuable guidance to NIST laboratory research programs for assessing future directions of the photonics industry as a whole.

b) ATP
In addition to the NIST laboratories, the ATP also has a history of close interactions with the OIDA, with several ATP staff routinely both attending OIDA meetings and workshops and giving presentations. Because the OIDA intersects such a large percentage of the U.S. photonics industry, ATP outreach activities at OIDA meetings provide an excellent mechanism for alerting large segments of the photonics industry to the existence of ATP as a potential funding source for cutting edge technology development.

E. NIST Laboratory Research Opportunities

There are several groups at NIST that are working on areas identified as near-term or long-term needs for SSL. In addition, there are other groups that could use their expertise in microelectronics to address similar issues in photonic semiconductor systems and

devices. In the outline below, we highlight some of the topical areas important in SSL that scientists at NIST could address for both the near term, i.e., one to five year period, and the long-term, i.e., five to ten year time frame.

1. Inorganic devices

- Large area substrates, buffer layers and wafer research
    i. Uniformity
        1. Across wafer uniformity
        2. Wafer to wafer uniformity
            a. Strain at buffer/substrate interface
            b. Surface finish and structure
    ii. Defect structure
        1. Defect identification
        2. Cluster behavior
- High-efficiency semiconductor materials
- Reliability and defect physics for improved emitter lifetime and efficiency
    i. Defect identification
        1. Sources
        2. Effect on multilayer structures
    ii. Reliability
        1. Failure mechanisms
        2. Lifetime prediction
- High-efficiency phosphors and conversion materials
    i. Quantum efficiency
    ii. Reliability
        1. Thermal effects
        2. UV bleaching
        3. Degradation processes
    iii. Distribution of conversion material
    iv. Interface scattering
- Encapsulants and packaging materials
    i. Interface scattering
    ii. Reliability
        1. Thermal damage
        2. UV damage
        3. Degradation processes
- Electrodes and interconnects
    i. Adhesion
    ii. Local heating
- Measurement metrics and human factors
    i. Standards development
    ii. Color assessment
        1. Device inter-comparison
        2. Interface with human expectations

- Physical, chemical, optical modeling measurement, and experimentation for substrate and epitaxial processes
    i. Efficiency
        1. Self absorption
        2. Interface scattering
    ii. Mechanical loading
        1. Lattice mismatch effects
        2. Thermal loading
            a. Distributed
            b. Local
        3. Delayed failure
    iii. Chemical stability of very thin films
    iv. Index measurement
- Evaluate systems lifetime and performance characteristics
    i. Lifetime prediction
        1. Failure mechanisms
            a. Static and cyclic electrical and thermal loading
            b. Defects
                i. Perturbing effects
                ii. Generation and coalescence
    ii. Quantum efficiency degradation
        1. Over time
        2. At high current
    iii. Color control

2. Organic specific

- Substrates for electro-active organic materials research
    i. Improved work function
    ii. Increased charge injection
- High-efficiency, low voltage, stable materials
    i. Increased mobility
    ii. Increased light generation
        1. Reduced non-radiative recombination
        2. Enhanced reliability
            a. Thermal stability
            b. UV/blue degradation resistance
            c. Reduced sensitivity to water degradation
- Improved understanding of fundamental physics

III. PHOTONICS IN HEALTHCARE

A. Current Status

Although our understanding of both photonics and biology has made tremendous advances in the last few years, optical techniques have been used in healthcare applications throughout human history. From cave drawings that image deadly wounds via drawings of figures with arrows protruding from their bodies through descriptions of plague-generated lesions during the Middle Ages and the development of the optical microscope, optical techniques have been used to diagnose health problems and to monitor the progress of healing.

In light of the extensive history relating optical approaches to health monitoring and diagnosis, a comprehensive discussion of the entire range of optical techniques currently used in healthcare lies outside the scope of this document. Rather, we will focus on recent developments in which optical techniques are used in new ways as diagnosis, treatment, or monitoring tools. While many of these tools are associated with aspects of imaging, photonics approaches should not be considered as synonymous with imaging. As will be discussed, photonic tools are being developed for treatment and chemical diagnosis as well as for imaging. In this section we will address both techniques already being developed for clinical applications and approaches still restricted to the laboratory environment. The expectation is that many of the latter approaches will soon make the transition to clinical application as commercialization efforts mature.

Before the discussion of specific applications, it should be pointed out that, like all tools, optical techniques have both benefits and limitations (Table 3). In practice, most of the benefits and limitations are application specific. For example, surface applications

TABLE 3: Benefits and limitations of optical techniques

Benefits:

• Non-contact
• Multiple wavelengths
  - Variable penetration
  - Tunable absorption
• Micrometer resolution
• Morphological and chemical information possible
• Combine imaging/treatment into same instrument

Limitations:

• Limited penetration
  - Maximum penetration 10 cm in IR region
  - Maximum penetration occurs for minimum resolution
• Contrast agents required

of optical techniques, i.e., those for the skin or eye, can usually be viewed as non-contact. However, for internal imaging, the limited penetration depth of optical techniques usually requires optical probes to bring the source light into the region to be interrogated, thus losing the non-contact aspect. Similarly, without the use of probes, the benefits of variable wavelength range are limited; typically, to achieve greater penetration, specific wavelengths are used, thereby pre-determining resolution and optical interaction with features of interest. Conversely, tuning the interrogation wavelength to interact with a specific feature of interest automatically places restrictions on the possible penetration depths. If the applications are intended to be used for diagnosis *in vitro* rather than *in vivo*, these restrictions are considerably relaxed, since penetration depth is less of an issue.

1. Clinical:

The development of lasers and light emitting diodes has had a major effect on medical treatment. From retinal mapping, eye surgery and epidermal ablation to more prosaic hair removal, lasers are routinely used for a range of surface medical treatments. Concurrent development of optical fibers has led to internal imaging capabilities such as endoscopy, permitting inspection of intestinal and esophageal passages to detect cancerous and precancerous conditions, and laparoscopy, allowing examination of abdominal and ovarian cavities. Combining laser sources and fiber catheters has given rise to capabilities such as laser angioplasty, in which plaque deposits are destroyed by focused optical radiation. In addition to these techniques, major advances in the understanding of cell chemistry for both healthy and diseased cells have resulted in increasingly sophisticated spectroscopic analyses of blood and tissue samples. *In vitro* tools are currently being used for a variety of applications: e.g., to check glucose levels for diabetes monitoring, to detect troponin T and myoglobin as a monitor for heart attacks in real time, using turbidimetry for distributed clot detection.

2. Research and Development:

Although the words *in vivo* and *in vitro* are used throughout the medical and biological communities, their precise meanings are somewhat context dependent. While *in vitro* means “in glass”, i.e., in a laboratory setting, and *in vivo* means “in life”, i.e., in a living body, the distinction is somewhat blurred. Some scientists consider studies of fixed cells to be *in vitro* and studies of living cells to be *in vivo*. In contrast, other scientists consider the study of living cells removed from a host to be *in vitro*, because they are in an artificial environment, and the study of cells in a living creature, e.g., mouse, human, to be *in vivo*. For this document, we use the latter definition; i.e., living cells that have been removed from their host are considered *in vitro* and not *in vivo*.

a) *In vitro*

While the predominant goal for research into biophotonics is the development of tools to be used eventually *in vivo* for healthcare,[12] there are a number of technical advances that

will almost certainly be limited to *in vitro* applications but that, nonetheless, will provide new understanding of life processes. This understanding will include both the behavior of healthy tissue as well as cellular and sub-cellular behavior associated with the onset of disease. The results of such an understanding could lead to the development of *in vivo* tools and procedures for identifying and treating diseases such as cancer at the very onset of cellular damage, i.e., low grade dysplasia. For the *in vitro* research areas, photonic activities are divided into three components: Optical Microscopy, Spectroscopy, and Combinatorial approaches.

i. Optical microscopy:
Advances in optical microscopy have made it possible to image features on the 100's and even 10's of nanometer scale. Taking advantage of the nonlinear optical properties of biological material, in some cases new techniques have been able to make use of contrast mechanisms that do not require dyes or external tracers. In other cases, optical tracers that are designed to attach to specific cellular sites, providing optical contrast through mechanisms such as fluorescence provide information regarding cellular dynamics. Finally, optical tools have been developed that allow manipulation of cell components on the micrometer and sub-micrometer level. While most of the tools that use these techniques can be purchased from commercial vendors, new applications are continually being devised and reported. The following is an overview of optical microscopy procedures being developed specifically directed towards healthcare.

- Confocal microscopy: This technique is a commercially available instrument that varies from traditional microscopy in that a scanned, focused laser beam and a pinhole spatial filter are used to provide high resolution both in the plane of the image and perpendicular to the image (i.e., in the axial direction). The principle advantage of the technique is that high resolution in the axial direction allows sequential images to be made at different focus depths into the specimen. Available software is able to combine these sequential planer images to generate a three-dimensional image.

  It has been shown that the lateral resolution and axial resolution of confocal microscopy can be $\lambda/3.7$ and $\lambda/1.2$, respectively, where λ is the wavelength of light used to generate the images.[13] A disadvantage of the confocal microscope is that, while the pinhole in front of the detector provides spatial filtering for the light scattered from the specimen, the light incident on the specimen has no depth filtering. Therefore, scattered light at any depth that is aligned along the optical axis co-axial with the pinhole is convolved into the raw image, generating noise and reducing resolution.[14] Numerical deconvolution procedures can, in principle, enhance this resolution[13] to the order of 100 nm, but require an additional step and inherently involve modifications to the original data. An additional limitation of confocal microscopy becomes evident when fluorescent markers are used. Because the energy required to excite the fluorescence must be greater than the energy of the excited photon, the source wavelength must be shorter than the wavelength of the excited photon. However, photon scattering and concomitant signal loss increase with decreasing wavelength. Therefore, while confocal

techniques can generate 3-D images of fluorescing sites, the depth within the specimen from which the information is obtained decreases as the energy of the fluorescent photon increases.

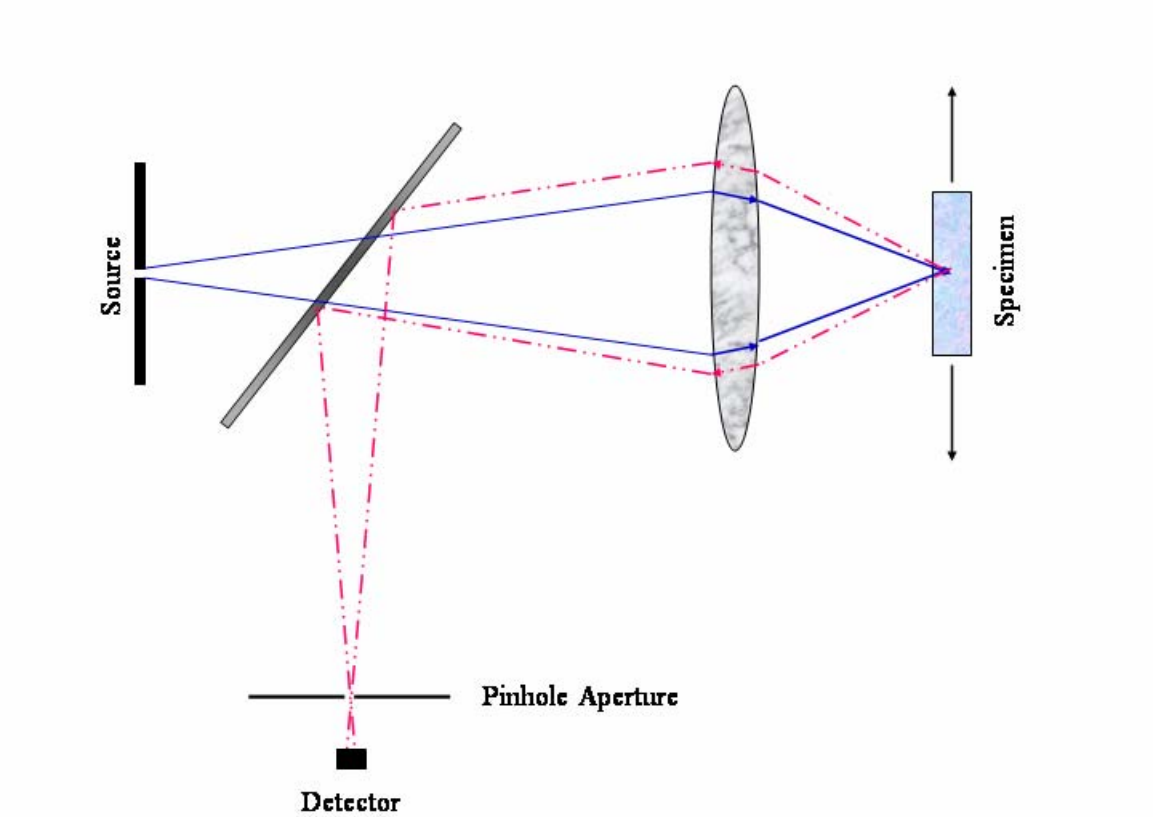

Figure 3: Schematic of a confocal microscope. The spatial filter in front of the detector provides resolution. Three-dimensional images can be generated by scanning the specimen at different focus positions within the specimen.

- Multi-photon imaging: In this procedure, which is increasingly seeing use in research laboratories for both basic research and pharmaceutical development, fluorescent markers are excited by the simultaneous absorption of multiple, lower energy photons from the excitation source. Usually, the markers and the excitation source are chosen such that two photons are adequate (i.e., the sum of the energies of the two photons is enough to excite the fluorescence), although there is recent work investigating three photon imaging.[15] The probability of two-photon capture by the marker is reduced by about a factor of 10^6 from the probability of single-photon capture for equivalent total photon energy.[15] The probability of three-photon capture is down by an additional factor of 10. In order to obtain the high photon flux required to achieve multiphoton excitation, a well-focused, mode-locked (e.g., femtosecond) laser is used as the source. Specimen damage due to the increase in laser flux is reduced by three effects: 1) the laser pulse width is very short, and, consequently, the average power is low, 2) the

longer wavelength of the exciting laser is not efficiently absorbed by the specimen, and 3) the region of high flux is limited to the focused beam waist.

Use of a multi-photon system results in very narrow depth resolution without many of the problems associated with normal confocal microscopy. The advantages of multiphoton imaging derive from the fact that no fluorescence will occur in the absence of simultaneous multiphoton absorption and the probability of that occurring goes as the fourth power of the intensity. Consequently, signal intensity resulting from excitation occurring before or after the focal spot will be negligibly small compared to the signal from the focus. Therefore, **a major source of noise in confocal microscopy is eliminated in multi-photon microscopy**.

An additional opportunity for multi-photon imaging takes advantage of both two-photon and three-photon absorption. If two markers are used in the cell, one that requires two-photon absorption and one that requires three-photon absorption, two separate portions of a cell can be monitored simultaneously and potentially, interactions can be observed in real time. A disadvantage of multi-photon microscopy is that the low absorption of the incident wavelength means that a background image (i.e., a non-fluorescing image) may not be visible for reference.

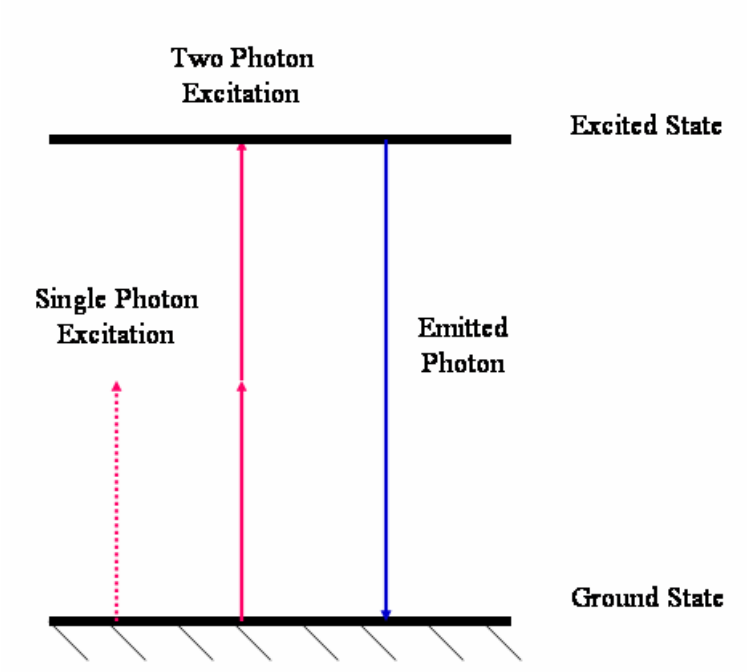

Figure 4: Energy diagram of two-photon process. Excitation wavelength is longer that emitted wavelength; a single incident photon has insufficient energy to excite an electron and is not absorbed.

- Second- and third-harmonic generation:[14-18] While higher-order harmonic generation has been studied in the photonics community for many years, its

application to biological systems is still limited to basic research applications. The process involves incident light interacting with a material having nonlinear optical properties, resulting in a conversion of the incident light frequency to a higher harmonic value. The technique is, in some ways, superficially similar to multiphoton absorption although the physical principles involved are quite different. The apparent similarities arise because, in both cases, the light from the specimen areas of interest is at a different wavelength than the incident light and a combination of second- and third-harmonic generation, like a combination of two-photon and three-photon absorption, can result in different portions of the specimen being imaged by different wavelength light simultaneously. However, in second- and third-harmonic generation, the change in wavelength results from optical nonlinearities in portions of the specimen itself rather than excitation of fluorescence. In addition, for second- and third-harmonic generation microscopy, the incident light can generate an image of the portions of the specimen that do not generate higher-order harmonics. Another advantage of this procedure is that it does not require the presence of dyes or other markers that have potential viability consequences in the specimens. A disadvantage is that the specimens themselves must inherently have non-linear optical properties. However, a wide range of biological structures generates higher-order harmonics: e.g., cell membranes, muscle fibers, and nerve fibers.[17,18]

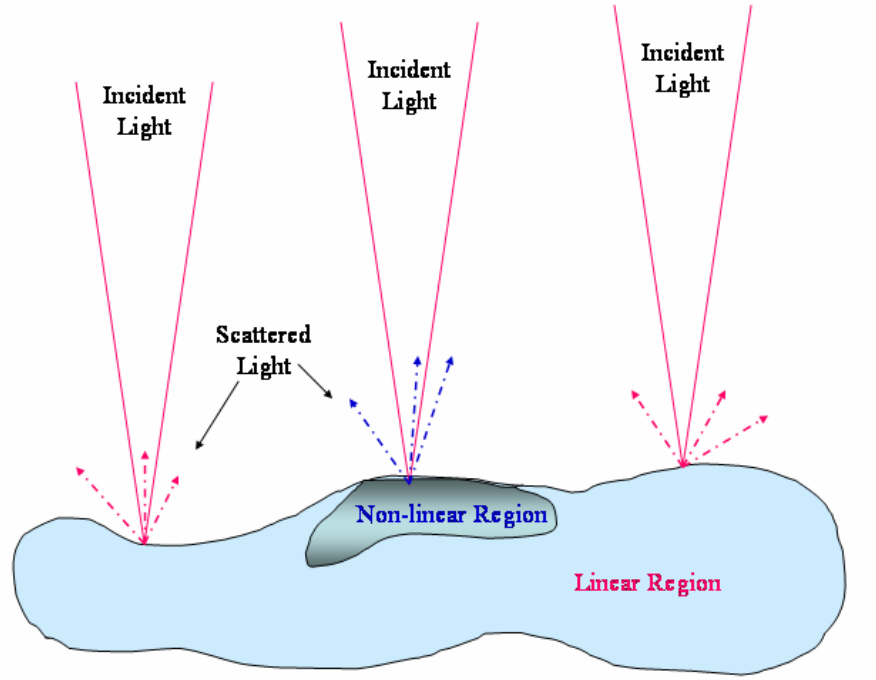

Figure 5: Incident light on the nonlinear region results in scattered light at twice (2nd harmonic) or three times (third harmonic) the frequency of the incident light.

Another issue that may limit the applicability of this technique is that higher-order harmonic generation in materials typically requires high incident flux. This can be achieved in a manner similar to the multiphoton absorption approach by using

a microscope objective to focus the incident light into a small volume at the region of interest. However, unlike the multiphoton absorption approach, which uses an incident wavelength that is not strongly absorbed, the higher harmonics approach requires strong interaction between the material and the incident wavelength. Therefore, care is needed to avoid photo-damage to the specimen.

- Fluorescence resonance energy transfer (FRET): FRET is a microscopy technique widely used in cellular biology research – both basic and applied. The technique uses two fluorescent markers and a laser source to image interactions between cellular components (e.g., two different proteins) on the nanometer scale.[19] One cellular component is tagged with one fluorophore and a second is tagged with the second fluorophore. The wavelength of the laser source and the optical properties of the two fluorophores are carefully chosen such that the laser wavelength, λ_l, will excite fluorescence λ_{f1} in the first fluorophore but will not excite the second fluorophore. However, when the two fluorophores are close enough together, a resonant energy transfer will occur between the excited first fluorophore and the non-excited second fluorophore resulting in fluorescence from the second fluorophore at λ_{f2} and a decrease in the intensity of λ_{fl}. Monitoring the intensity of λ_{fl} and λ_{f2} during an experiment provides information regarding the conditions affecting interactions between the two cell components.

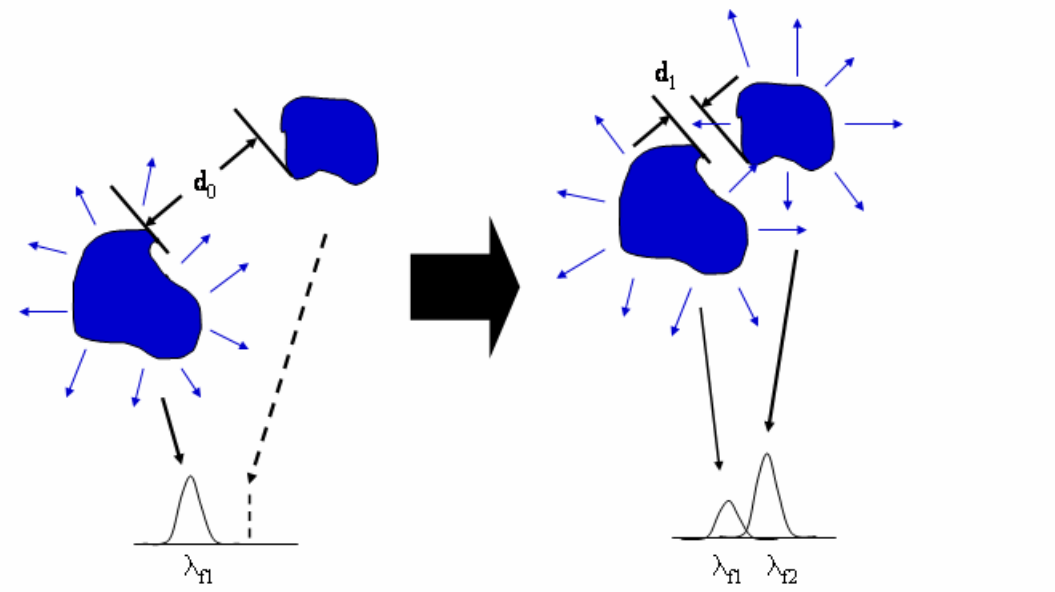

Figure 6: Schematic of FRET. As the two particles approach each other, the laser-induced fluorescence in the dye in particle 1 induces a secondary fluorescence in the dye in particle 2 through non-radiative dipole interactions.

The primary advantage of FRET is its extreme sensitivity to the spacing between fluorophores. Because the energy transfer is a non-radiative resonance phenomenon, it is very short range and the efficiency of the transfer is strongly dependent upon the separation between the cell components. Measurements of the intensity of λ_{fl} or λ_{f2} can

give very precise information regarding that separation; monitoring the polarization of the emissions can give information regarding relative orientations. A disadvantage of the technique is that interactions between cell components must be inferred and the type of interaction is unknown. In addition, the effects of the fluorophores attached to the components on their subsequent interactions are unknown.

- Total internal reflectance (TIR): TIR is being developed to provide images and information in very restricted regions of a cell. The technique involves placing the region of interest, e.g., a cell membrane, very near a planer waveguide. As light is transmitted through the waveguide, interactions between elements near the membrane can interact with the evanescent waves leaking from the waveguide; because the interactions are with evanescent waves, they are strong functions of their distance from the waveguide.[20] Typically, luminescent tags are attached to the cell components of interest and interactions are inferred from the intensity and distributions of the luminescence sites. Many of the advantages and disadvantages of this technique are similar to those discussed for FRET.

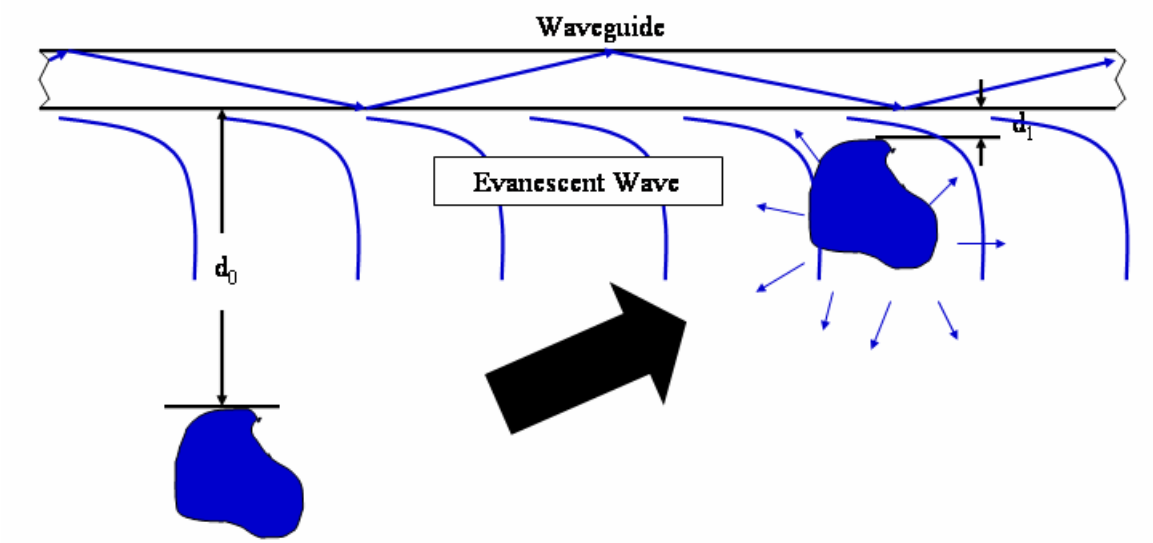

Figure 7: Schematic of TIR fluorescence

- Near-field scanning optical microscopy (NSOM): NSOM provides nanometer to tens of nanometer lateral resolution through the use of the illuminating aperture, e.g., a drawn optical fiber, being placed within nanometers of the specimen surface. Under these conditions, i.e., both the separation of the light source from the specimen and the dimensions of the illumination aperture are much less than the wavelength of the illuminating light, the resolution is defined by the aperture size. While NSOM is an increasingly widely used technique in materials, there are a number of difficulties associated with using it for biological specimens,[21] either fixed, i.e., treated with chemicals to generate a rigid, cross-linked structure, or living. One problem is that biological specimens are not flat on the nanometer scale. Consequently, maintenance of the spacing between the illumination aperture and the specimen can be quite difficult as the specimen is scanned. A

similar issue is that biological specimens are not thin on the nanometer scale and, in addition, biological cells are usually filled with water. Therefore, the feedback forces required to position the NSOM can drive objects of interest out of the field of view in living cells. NSOM can, in principle, be combined with spectroscopic techniques such as fluorescence (e.g., FRET) techniques[22] or Raman spectroscopy[23] to provide additional information. However, the low light levels in NSOM make spectroscopy challenging, particularly for Raman measurements, which are inherently inefficient.

- Fluorescent markers: Frequent reference has been made above to optical tracer and fluorophore tags in the various optical microscopy techniques. Materials such as fluorescent particles,[24] fluorescent proteins[25] and quantum dots[26,27] have been and are being developed that will attach to specific proteins or other cellular features to provide a signal for optical microscopy. Issues associated with similar tracers for a wide range of *in vivo* applications will be mentioned later. On the cellular, *in vitro* level, these tracers are now making it possible to monitor time-dependent processes in living cells. However, the questions of toxicity, specificity, and more subtly, whether the biological functions are modified by perturbations due to the attached materials remain unanswered and objects of concern.[28,29]

- Optical manipulators: Although not limited to optical microscopy, a couple of recently developed optical tools used in microscopy should be mentioned: optical scalpels[30,31] and optical tweezers.[32] Optical scalpels are focused laser beams used to cut biological tissue. Although this is not a new idea, it has in recent years been extended to microsurgery on, and within, individual cells. Lasers are being used to open and reseal cell membranes, liposome membranes, and even human chromosomes.[33] This ability would be of limited use without the simultaneous development of tools like optical tweezers. Optical tweezers use forces generated by the electric field gradient of a focused laser beam to entrap and move small particles. The particles can range from a few nanometers to several micrometers. This size range makes optical tweezers an excellent tool for moving biological components within a cell, e.g., the nucleus, or even the cells themselves. The combination of optical scalpel and optical tweezers makes it possible to insert or remove material from within cells or within organelles, to attach components, e.g., proteins, onto other cell components, and even to dissect macromolecules within cells.

ii. Spectroscopy:

A number of the techniques mentioned above are powerful tools that can provide much more information than is contained in optical contrast images. For example, Raman, near-field Raman, fluorescence, and light scattering measurements can all be used spectroscopically, i.e., as a function of wavelength, to provide chemical, orientation, and structural information in addition to the time-dependent location information that images provide. The combination of spectroscopic information with imaging information has the potential of providing detailed information regarding intercellular and intracellular

mechanisms under varying conditions. Currently, however, spectroscopic tools are predominately used independently of imaging techniques in their traditional role of performing chemical assay, albeit at increasingly reduced size scales. Sample sizes are being reduced to μliters, and under carefully controlled laboratory conditions, even single molecules have been interrogated.

iii. Combinatorial approaches:

The enhancement of spectroscopic techniques that allows single cell or even sub-cell interrogation makes it possible for researchers to apply parallel measurements to reduce noise[34] or quickly to evaluate new markers or drugs under differing conditions.[35,36] One of the easiest approaches is to use optical fiber arrays, applying separate fibers to individual cells. In this way, identical measurements can be made simultaneously on identical cells to reduce noise within a measurement, or individual cells can be modified, e.g., to contain a different marker or modification of a drug, and a wide parameter space can be mapped rapidly. The measurements can be as simple as monitoring fluorescence intensity or as sophisticated as measuring entire Raman spectra for each fiber. An alternate approach that does not require fibers could make use of uniform illumination of an array of cells or sub-cellular components. The scattered light from the specimens could then be individually imaged, via an array of micro-lenses, onto an array detector, or, alternatively, the light could be scanned rapidly into a single detector. All of these approaches have the advantage of high-speed assessment capability. However, there are also limitations. The major limitation is spectroscopic techniques provide a great deal of data on each cell but **there is currently no mechanism for rapidly quantifying, assessing, and efficiently accessing all of the chemical and structural information obtained for each element of the array when a large array of data is being obtained with rapid throughput**.[12] Therefore, while in principle a great deal of knowledge could be obtained regarding marker or drug interactions within a cell under various conditions, typically such data are not obtained. Rather, a spectroscopic peak is chosen and its intensity, position, or width is monitored for each element of the detector array and the remaining data are discarded.[37] This leads directly to the second limitation of the technique. The procedure requires a precise knowledge of the type of interaction to be investigated. Without this knowledge, simultaneous relevant processes that occur may not be detected.

b) *In vivo*

Challenges associated with *in-vivo* measurements are of a different nature than those found in *in-vitro* work. In particular, the primary goal of *in-vivo* research is to develop procedures that will not generate more damage in the host than the intended treatment cures. The second goal is to generate sensing schemes that will detect specific responses, via imaging or chemical sensing techniques, in an inhomogeneous environment that has a

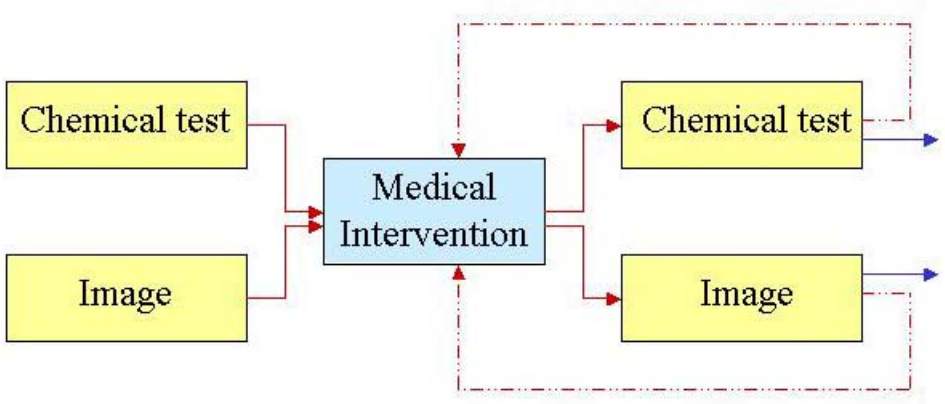

Figure 8: Flowchart showing sequential, semi-independent relationship between diagnosis, intervention/treatment, and treatment evaluation in current medical practice.

dynamic background filled with a wide range of chemical species, pH values, densities, sizes, and optical properties. The third goal is to improve understanding of the interworkings of the living system, thereby developing criteria for earlier, more precise, disease indicators and minimizing the extent of required medical interventions. Current procedures generally use a chemical test or some form of an image to detect a problem, then, if feasible, an image to localize the problem, a medical intervention, and finally, an image or chemical test to evaluate the consequences of the intervention (see Figure 2). Consequently, we will divide the following discussion into the categories of Imaging, Diagnosis, and Treatment.

i. Imaging:
Because of the difficulties listed above, a living body is a very difficult object in which to discover defects via photonic imaging. Problems are minimized to some degree in procedures such as x-ray imaging of bone, because the penetration of the x-rays is relatively high in a living creature and the contrast between the high density, high atomic number (i.e., high capture cross section) bone and the low density, relatively low atomic number soft tissue allows for good signal intensity and reasonable high contrast. However, use of visible optical techniques to obtain images is much more difficult. Water and hemoglobin in the body combine to absorb light over the entire near-UV to near-IR range[38] with the exception of two windows centered at approximately 800 nm and 1200 nm. In these windows, light can penetrate about 12 cm. However, for wavelengths of 700 nm, 600 nm, or 500 nm, the penetration depths resulting in half the initial intensity are 10 cm, 1 cm, and 0.5 cm, respectively (see Figure 3). Clearly, there is a trade-off between resolution and penetration depth, with penetration depth falling off dramatically as wavelength decreases. However, absorption is only one of the factors governing the use

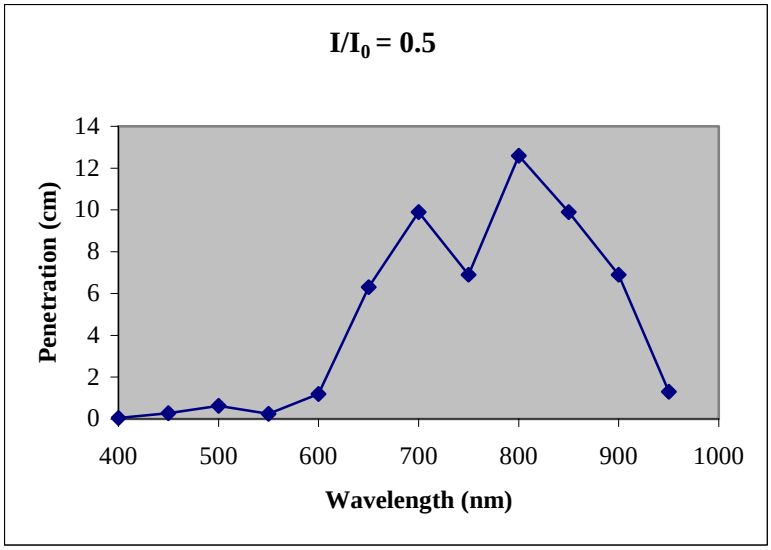

Figure 9: Penetration depth through water and hemoglobin across the visible wavelength range. Values represent the depth at which the intensity is 50% of the original value.

of visible or near visible optical techniques *in vivo*. The second major limiting factor in using optical techniques is that bodies are highly heterogeneous systems, filled with scattering objects ranging in size from tens of nanometers, e.g., membranes, to objects such as organelles and whole cells on the tens of micrometers scale. Consequently, even in the absence of absorption, reflected and transmitted signals are highly attenuated due to multiple scattering events at all wavelengths. Finally, living bodies are not static. Muscles twitch, blood flows, chemical processes occur. Therefore, any optical technique used *in-vivo* must be designed to accommodate such motion, or else must be limited to detection of defects large compared to the scale of motion-induced displacement.

- *Optical scattering* One of the most rudimentary spectroscopic tools is the measurement of transmission as a function of wavelength. However, because of the heterogeneous nature of a biological body, and the wide size scale over which the heterogeneous features occur, as mentioned above, scattering of the incident light is impossible to avoid. Consequently, the use of transmitted light to image internal objects such as tumors has not been pursued in the past. However, with the advent of better near-IR sources, detectors, more powerful computers and, especially, models that incorporate detailed descriptions of how different wavelengths interact with tissue, optical scattering techniques are beginning to be developed for internal diagnosis applications.[39] Even with improved theory and measurement procedures, absorption and scattering lower the signal intensity and reduce contrast to the point that lesions/tumors below 5 mm are difficult to detect. However, on the positive side, the use of multiple wavelengths allows spectroscopic information to be obtained. Consequently, information regarding different components that make up the body, e.g., water, hemoglobin, and lipids, can be acquired through multiple scattering measurements.

- *Fluorescence* As discussed previously, advances in fluorescence techniques already provide extraordinary insight into cellular reactions in the lab and hold the promise for making similar contributions as diagnostic and health monitoring tools *in vivo*. Use of fluorophores such as fluorescent particles,[24] proteins[25] and quantum dots[26,27] that can be targeted toward specific proteins, organelles, or, within a body, specific organs, inflamed joints,[40] or tumors opens tremendous opportunities ranging from basic research into cell behavior and chemistry through applications in diagnostic and treatment monitoring. In addition, the increasing possibility for development of new markers that identify the onset of diseases afflicting specific subset populations holds the promise of "personalized medicine". Primary challenges to this vision are difficulties associated with developing a wide array of biomolecular tracers for the different possible applications. Not only are there difficulties associated with each tracer creation, i.e., the identification of a tracer as well as the associated reliability, specificity, and failure mechanisms, and increasing awareness of toxicology issues, but, as medical diagnosis tools become increasingly directed toward smaller population sizes, the cost of such tracers must be borne by a continually decreasing number of individuals. The tradeoff between cost and population is already affecting diagnostic tracer development.[41] A separate issue that needs to be addressed for fluorescent imaging *in vivo* is the need for improved resolution. Whereas resolution *in vitro* can be sub-micrometer, *in-vivo* resolution is many centimeters or, at best, many millimeters. As better understanding of cell chemistry makes possible disease detection at earlier stages, the resolution limitations of fluorescence imaging will have to be improved for the improved knowledge base to result in a decrease in the severity of medical intervention.

- *Optical coherence tomography[42-46] (OCT)* Optical coherence tomography is an imaging tool that provides high lateral and depth resolution. The technique uses an interferometer with a moving reference mirror to obtain depth information. Depth resolution is inversely proportional to the band width, so a low time coherence light source such as a superluminescent optical diode is typically used as a light source. The resultant high resolution is one of the principle benefits of OCT, which is able to provide sub-cellular information even *in vivo*. Developed initially for inspection of the eye, OCT procedures are being developed that will extend the technique to the esophagus and even the circulatory system. The eye, containing a transparent portal, allows OCT interrogation of several millimeters. However, in other applications, penetration depths are limited to a millimeter or less. The limited penetration poses the most critical limitation on OCT. While OCT has the resolution and the spectroscopic capabilities to detect the onset of lesions at a very early stage, it can only see surface or near-surface features. The second important limitation of OCT, paradoxically, is related to its high resolution. OCT gathers so much information on such a fine scale that: 1) it is difficult to sort through all of the data and 2) it is difficult to identify the precise location in the body at which medical intervention (e.g., a surgical tissue removal) is needed. At this time, there is no known solution to the penetration depth barrier to OCT. However, the "data glut" problem is being investigated with a multi-

modal approach that combines OCT with another imaging tool of lower resolution. The alternate imaging tool can scan the area, and when an indication of a potential problem is observed, the OCT can be used to conduct a high resolution scan of a limited area. Alternatively, both scans can be conducted simultaneously and the lower resolution tool can be used to register the location of the OCT data.

ii. Diagnostics:

Optical tools in use or being researched for *in vivo* diagnostics typically fall into one of two categories: imaging[47] or spectroscopy[48]. Imaging, by far the most widely researched aspect of optical diagnosis techniques, is used, often with disease or organ specific tracers, to generate high contrast images for diseases detection and concomitant size and location information. By making measurements over time with a contrast agent or molecular tracer, relative severity of the disease can sometimes be assessed. However, the information is typically visual only and, consequently, relatively qualitative in nature. Spatial dimensions can be obtained but detailed information will still have to be determined by a biopsy. Spectroscopy tools, i.e., tools used to obtain chemical information rather than images, are being recognized as potentially very powerful for *in-vivo* applications but are still relatively rare. As mentioned previously, when spectroscopic tools are used for imaging, e.g., fluorescence or Raman spectroscopy, typically a major peak position or intensity is monitored and the remaining information is discarded for processing speed and data storage reasons.[37]

iii. Treatment:

As might be expected, photonic tools in medical treatment lag behind those being developed for imaging and diagnostics. One treatment with potentially broad applications is photodynamic therapy (PDT). In PDT, light sensitive agents, e.g., systemic photosensitive dye, quantum dots (QDs), nanoscale spheres, collect at a region of interest such as a tumor. A laser or high intensity diode lamp illuminates the region either locally activating a toxin or generating local heating that kills the surrounding tissue. Although the technique has clear benefits, there remain a number of issues that must be addressed. First, monitoring the dosage of the optically active agents relative to the dosage[49] required for treatment in absolute terms and as a function of time is difficult. Second, systemic dyes are undesirable because the patient remains light sensitive until the body eliminates the dye, which can take several hours or even a few days for complete elimination. Third, as mentioned previously, the material composing most QDs is toxic. The QDs can be coated but the lifetime and reliability of the coating in the chemically active environment of the body as well as during optical heating must be ascertained. Nanoscale spheres made of Au, alumina, or polymers are more inert, although the long-term biological response to these materials is not known. Equally important for all of the nanoscale materials is the fact that both their dispersal in the body and their optical absorption are strongly dependent upon sphere size. Therefore, material issues such as purity, size, size distribution, agglomeration, and reactivity must be controlled very well.

B. Long-term issues

Long-term issues associated with healthcare are predominately related to safety, reliability, efficiency, and effectiveness. In addition, there is a growing sense that the traditional distinctions between imaging/detection, diagnosis, and treatment will become blurred in the future. Figure 4 shows schematically this blurring of previously independent aspects of medical treatment. As mentioned previously, current medical practice typically separates diagnosis, treatment, and evaluation into distinct categories. Frequently, practitioners in the three categories do not even speak together; written reports are passed between them or placed on the patient's chart. Consequently, subtle effects in diagnosis or changes in treatment may not be communicated among the different groups of people, leading to confusion in treatment. **Improvements in imaging and spectroscopic techniques are expected to provide true chemical information across the entire image and to provide it in real time.** Such capabilities could lead to *in-situ* biopsies, real time analysis during intervention (e.g., surgery, PDT), and immediate post-treatment biopsies. Increased knowledge of the chemistries associated with precursors to disease coupled with spectroscopic imaging on the sub-cellular level might even allow detection, treatment, and follow-up of pre-cancerous areas without the need for traditional surgical procedures even arising.

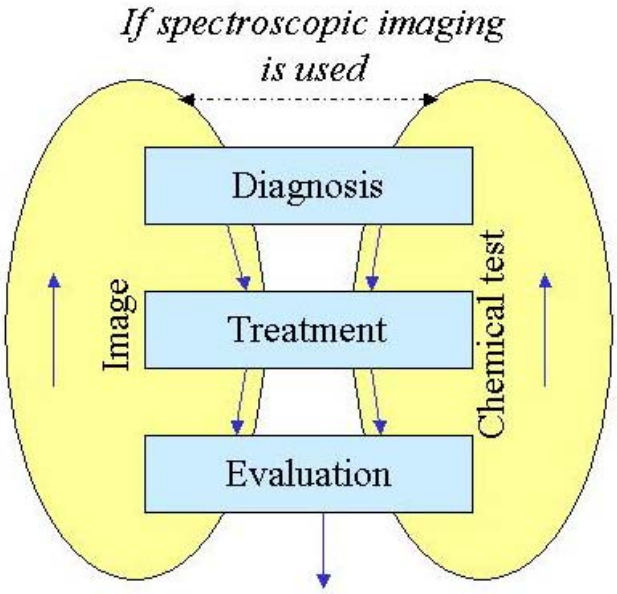

Figure 10: Schematic of future use of photonics in medical care. Advances in both imaging and spectroscopy procedures will a linking of the formerly distinct areas of Diagnosis, Treatment, and Evaluation into a more monolithic structure. As spectroscopic imaging tools improve to allow chemical analysis across entire images, distinctions between imaging and chemical tests will tend to disappear, as well.

1. Implant/biotracer/imaging agent issues:
The long-term issues associated with insertion of foreign material into the body are similar to those discussed above for short-term tests. The primary concern is for biocompatibility.[12] What are the degradation mechanisms?[50] What occurs at the interface between the body and the implant? What time frames are important? What are the failure probabilities and implications? Are there fouling mechanisms that need to be considered? With nanoparticle tracers, the time frame in the body is intended to be on the order of hours or days. Yet, some of the nanoparticles may become trapped and remain indefinitely. For those materials and their debris, the toxicity issues touched on previously remain important, and moreover, the time frame over which interactions must be considered is extended considerably. Some of the parameters that need to be monitored for toxicity assessment are:[51] composition, size, shape, deformability, stability, and coatings.

2. Imaging/spectroscopy:
As shown in Fig. 4, a long-term goal for imaging is to combine real-time spectroscopic information with image formation. Implied in that goal is the need to develop a direct relationship between measurements and cellular behavior.[37] A second critical long-term need for imaging that is expressed by everyone from the pharmaceutical industry through diagnosticians, all the way to the FDA is the need for standards, procedures, and techniques that will provide validated image interpretation.[52] Among the necessary improvements are instrument-to-instrument reproducibility, operator-to-operator reproducibility, and even reproducibility of the same operator on the same instrument and the same patient from one measurement to the next.[40] In fact, there appears to be a widespread sense that image analysis tools need to be developed to the extent that the judgment of the human operator can be removed from the image analysis process.[40,52] This goal implies that interactions of the physics, chemistry, biology, and statistics used to create the image need to be more rigorously understood to allow automation of image analysis.[12] Combining these requirements, the future of imaging requires, on its simplest level, that:

1. the engineering of the instrumentation must be well enough defined that images made of standard reference specimens on instruments from different manufacturers or different models from the same manufacturer can be related in a meaningful and understandable way;
2. analysis algorithms must provide at least a core set of imaging tools common to all instruments to allow image comparisons between instruments and to confirm consistency

and on a more sophisticated level, that:

1. the image probe should provide cellular and sub-cellular chemical information;
2. the information should be directly connected to cellular processes of interest;
3. the information should provide quantitative information regarding the presence or absence of a disease and, if present, a measure of the disease progress.

The implications of the last three items are that **detailed spectroscopy information needs to be obtained as part of the image**. This, in turn, requires that spectroscopic techniques need to be improved in speed, signal/noise, and spatial resolution for them to be useful as imaging tools on the cellular level while retaining their use as spectroscopic instruments.

In addition, because these data sets will contain three-dimensional coordinate information, spectra containing up to 1000 points of wavelength *versus* intensity (and possibly phase) information, possibly a temporal axis, and fitting parameters, data handling tools need to be developed to optimize data storage, data retrieval, and data viewing, as well as general data manipulation for n-dimensional data sets. Finally, data analysis techniques need to be standardized and automated. While relatively large, isolated peaks can be fitted automatically with reasonable accuracy, analysis of complicated spectra still requires operator input and judgment. This last statement leads to a point only recently recognized; all image analyses should include quantitative, standardized, and well-defined uncertainty discussions and medical practitioners need to be trained to understand those discussions.

C. NIST Interaction Opportunities in Photonics in Healthcare

Unlike SSL, which is predominately a commercial driven activity that also has benefits to society at large in terms of increased energy efficiency, increased reliability, and reduction in greenhouse gas production, healthcare is viewed as primarily a matter of public safety and only secondarily as a commercial enterprise. Consequently, the area of photonics in healthcare is dominated by government agencies tasked with the responsibility of assuring safety and effectiveness of medical treatment and is less driven by large consortia of businesses. This is not meant to imply that business does not play a large role in healthcare in the United State, from large pharmaceutical companies down to small start-ups, nor does it mean to downplay the importance of university research, particularly those universities with associated teaching hospitals, in medical R&D. However, for the subject of Photonics in Healthcare, unlike SSL, it is difficult to isolate one or two consortia that drive research directions and guide government agencies that monitor this topic. Rather, two government agencies, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) function as the primary drivers for progress through their funding and regulatory practices. These two organizations act as the main mechanism for research concepts and devices to reach commercialization. A third organization, the National Science Foundation (NSF) provides funding for research that is typically less applied.

1. Food and Drug Administration (FDA)

The FDA is a regulatory agency that monitors medicines, devices, and procedures for safety and compliance with regulatory requirements. Its mission involves assuring near-term and long-term safety and research conducted at the FDA is closely focused on this mission.

a) NIST Laboratories
Most of the work at the FDA is too applied and too near term for research collaborations between NIST and FDA to be easily formed. However, some areas of mutual concern are readily apparent; the FDA is highly concerned with reliability, degradation, degradation mechanisms, and lifetimes associated with any foreign material implanted or injected into the body. There are many materials and chemistry issues that could reasonably be addressed by NIST. In addition, there are a number of areas (e.g., OCT) in which the FDA would benefit from standards work and metrology that could be done at NIST. It should be noted that, because of the large level of device, drug, and treatment monitoring which is the ongoing responsibility of the FDA, external collaborations need to be directly related to the FDA mission.

b) ATP
The FDA could provide a large reservoir of reviewers, and potentially, ATP proposal evaluation board members who have an outstanding knowledge of current medical technology and associated barriers and pitfalls. The aspects of the FDA that make scientific collaboration somewhat difficult for the NIST laboratories (i.e., short term, applied research) provide the FDA scientists with an excellent view of needed improvements and recognition of innovative thinking regarding technologies soon to be introduced into the marketplace.

2. National Institutes of Health (NIH)

The National Institutes of Health are formed of a group of semi-autonomous Institutes, each of which has its own mission, typically, the study and treatment of a specific disease. Although most of these Institutes probably have applications that could be considered as biophotonics, it appears that bulk of the work on photonics in healthcare is funded by either the National Cancer Institute (NCI) or the National Institute for Biomedical Imaging and Bioengineering (NIBIB).

a) NIST Laboratories
Interactions with NIH benefit the NIST laboratories in three areas. First, NIH provides an important mechanism for generating collaborations between NIST scientists and the medical community, either NIH staff or researchers funded by NIH. This mechanism has been strengthened considerably by the joint NIST/NIH postdoctoral program. The second benefit of working with NIH is credibility. NIST is well recognized as a metrology laboratory but is not well known for its research in medical or biological applications. Therefore, collaborating with the medical staff at NIH provides that dimension of capabilities to the joint research. The third benefit is that proposals that advance both the health mission of NIH and the metrology mission of NIST can result in funding for equipment and guest scientists. It should be mentioned that there are a number of ongoing interactions between different groups at NIST and NIH.

b) ATP

Interactions with NIH benefit ATP in ways similar to those described for DOE in the SSL section. Not only does NIH form a source of potential reviewers for biology/health related ATP proposals, close relations with NIH provide insight into near-term and longer-term research and development issues associated with healthcare. In addition, it may be possible to develop a relationship with program managers at NIH in which they shepherd researchers who have commercialization proposals that are inappropriate for NIH funding toward ATP competitions. Finally, the NIH provides both the ATP and the laboratories an additional mechanism for outreach and education through the many workshops that the NIH provides on a wide range of current topics.

3. National Science Foundation (NSF)

The NSF is a government funding organization directed to providing resources for basic research. In this regard, the NSF might be considered on the opposite side of NIH from the FDA. The NSF is less concerned about commercialization than NIH and far more concerned with expanding the basic knowledge base than the FDA is.

a) NIST Laboratories

Although the NSF does not provide funding for NIST staff time, it does fund proposals that would cover guest scientist, travel, and publication costs. More importantly, the NSF has a huge number of contacts with colleges and universities and, consequently, could provide a great deal of information that would lead to collaborations between NIST staff and universities. The NSF can also provide an additional resource: information regarding current research trends.

b) ATP

As with other government agencies discussed previously, the NSF can provide reviewers for proposals. In addition, the NSF funds technology centers that act as incubators for new companies. Contact information for the NSF Center for Biophotonics Science and Technology is provided in Section VI: Appendix II.

D. NIST Research Opportunities

As mentioned above, there are a number of groups at NIST already involved in biophotonics research and active collaborations with NIH or other organizations. Some of the research issues in the outline below are being addressed by these groups. However, the listed items remain important topics to enhance current understanding of biological behavior in general as well as specific instrument/biology interactions. In addition, many of the topics listed below address metrology needs and, consequently fall directly into the NIST mission.

1. Imaging
    a. Resolution
        i. Signal/Noise (S/N)
            1. Physics of interactions

2. Statistical tools
3. Uncertainty analysis

ii. Contrast
1. Physics of interactions
2. Markers
a. Sensitivity
b. Specificity
c. Toxicity (material properties)
d. Uniformity
e. Material/tissue interface chemistry

b. Reproducibility
i. Operator to operator
1. Measurement protocols
2. Technique metrology (e.g., OCT, fluorescence, Raman)

ii. Single operator repeatability (same is operator to operator)

iii. Instrument to instrument
1. Measurement protocols
2. Standard sources, detectors
3. Calibration procedures

c. Spectroscopy
i. Spatial resolution
ii. Relationship to biological functions
iii. Sensitivity
iv. Data handling

2. Implants
a. Biological compatibility
b. Reliability
i. Degradation mechanisms
1. Encapsulation
2. Mechanical
3. Chemical
a. Interface interactions
b. Particle/ion diffusion

ii. Lifetime prediction
iii. Accelerated test procedures

3. Single cell investigation
a. Near field techniques
i. Metrology
ii. S/N
iii. Apply to living cells

b. Measurement physics relationship to biological function

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    - Organizations
        - OIDA, www.**oida**.org/
            - Reports
            - Workshop attendance
        - NEMA, www.**nema**.org/
            - Reports
        - Next Generation Lighting Industry Alliance, www.nema.org/prod/lighting/ solid/upload/NGLIA-fact-sheet.pdf
            - Reports
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VII. APPENDIX III: ATP funded projects

SSL:

Status	Project Number	Title
Completed	1998-02-0016	100-Millimeter Semiconductor Wafer Processing Technology for InP-Based Photonic Devices
Completed	1993-01-0205	Holographic Graded-Index, Non-Lambertian Scattering Screens and Components with Light-Shaping Capability
Completed	1991-01-0142	Manufacturing Technology for High Performance Optoelectronic Devices Based on Liquid Phase Electro-Epitaxy
Completed	1991-01-0263	A Feedback-Controlled Metalorganic Chemical Vapor Deposition Reactor
Completed	1991-01-0256	Advancement of Monocrystalline Silicon Carbide Growth Processes
Completed	1998-02-0058	Manufacturable Solid-State Lighting
Active	2004-1E-7011	Low Cost, High Efficiency Chip Scale LED Lamp
Active	2004-1E-7075	Processes for Growing Large, Single Crystal Aluminum Nitride

Photonics in Healthcare:

Status	Project Number	Title
Completed	1994-05-0004	Compact Blue Laser for Diagnostics
Completed	1994-05-0017	Molecular Cytogenetics Using the Genescope: An Ultrafast Multicolor System for Automated FISH Analysis
Completed	1994-05-0018	SBH Format 3 Megabase Diagnostics Instrumentation
Completed	1994-05-0030	Diagnostic Laser Desorption Mass Spectrometry Detection of Multiplex Electrophore Tagged DNA
Completed	1995-08-0012	Development of Bar Code Diagnostics for DNA Diagnostics
Completed	1995-08-0023	Arrayed Primer Extension (APEX): The Next Generation DNA Analysis System for Sequencing in DNA Diagnosis
Completed	1997-07-0001	Combinatorial Cell Culture: Tool Development and Application to Human Stem Cell Growth
Completed	1998-01-0154	Non-invasive Glucose Measurement Using Chemical Amplification and Optical Sensing
Completed	1998-01-0163	Development of Next-Generation OCT Technology
Completed	1998-08-0020	Multiplex DNA Diagnostic Assay Based on Microtransponders

Active	2000-1A-4106	Blood "Fingerprinting": A First Step Toward Personalized Medicine
Completed	2000-1B-4140	A Novel Intraoral Three Dimensional Digitizer for Digital Dentistry
Active	2001-1E-4406	Long-Term Implantable Optical Blood Glucose Monitor
Active	2002-3B-5694	Microsphere-Based Spectroscopic Instruments
Active	2004-1B-7002	Quantum Dots for Biomedical and Consumer Applications

VIII. APPENDIX IV: Benefits accrued to ATP detail

Benefits accrued to this ATP detail fall into three interrelated categories: benefits to the ATP, benefits to the NIST Laboratory, and benefits associated with personal development.

- Benefits to ATP include transfer to the Electronics and Photonics Group technical knowledge of materials science issues related to electronics and photonics applications, participation on the Electronics and Photonics Board during competition, extension of the ATP reviewer pool, and increased contact with other government agencies. In addition, the current state of the art in two emerging photonics areas, Solid State Lighting and Healthcare, has been analyzed and the information has been organized and disseminated to the ATP in both verbal and written form, along with listings of internal NIST and external government, industry, and university contacts. Finally, the detail has advanced interactions between the ATP and NIST Laboratories through both formal and informal interactions.
- Benefits to the Laboratories mirror those to the ATP to a large extent. Relationships that have been developed with other government agencies are potentially very valuable. Similarly, the information obtained on the two technical areas described in this document provides the Laboratories an opportunity to evaluate two emerging areas, including scientific and technical barriers, customers, economic importance, and sources of potential collaborators. While the benefits described heretofore were anticipated, benefits resulting from informal interactions between ATP staff and laboratory staff were more serendipitous but equally important. An example of such an interaction is the informal meeting between two Ceramics Division staff and two ATP staff at which generic issues associated with biomarkers were discussed. The discussion helped lead to a formal interaction between the Ceramics Division and NIH investigating nanoscale particle analysis.
- Benefits of combining NIST laboratory and ATP experience include the opportunity to work closely with groups of people with widely varying backgrounds. The opportunity to make contacts with people in other government agencies is potentially very valuable for the development future research projects. With respect to the areas of Solid State Lighting and Photonics in Healthcare, the knowledge gained in developing this report will, inevitably, remain much greater than the knowledge transmitted to the ATP or the Laboratories via formal written or oral presentations. However, even the knowledge not transmitted formally will find its way into future research projects as they evolve and, therefore, will remain very valuable. Finally, observation of the mechanisms by which the ATP operates, mission driven and criteria directed with a clear vision for technology transfer into the economy, has helped formulate a formalized evaluation procedure that can be used to assess future research choices in the NIST laboratories.