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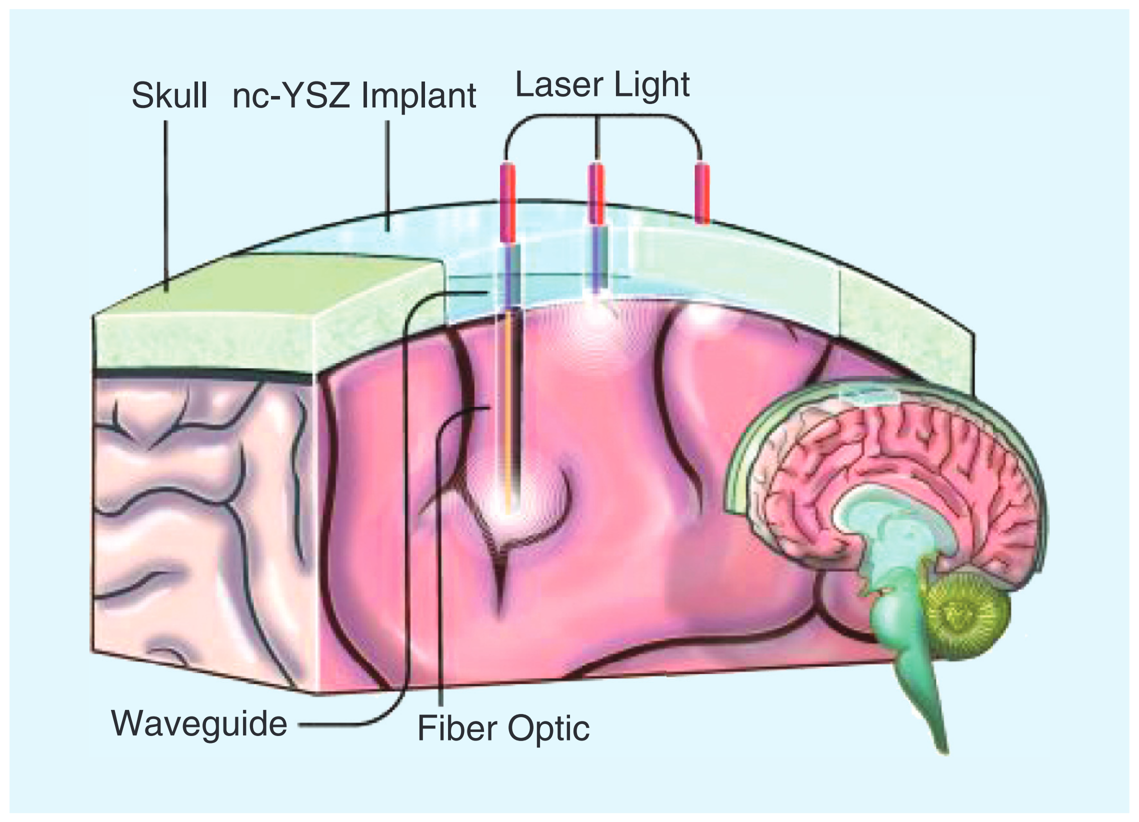

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A New Window for Photonics in the Brain

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Abstract—Current advances in materials processing have lead to the improvement in the optical properties of ceramics. In particular, nanocrystalline Yttria-stabilized-zirconia (YSZ) has shown to provide a novel platform for developing transparent cranial implants. In this article we present our ongoing research efforts for developing a platform to obtain optical access to the brain tissue. This "Window to the Brain" (WttB) is expected to provide a means to extend the reach of photonic tools for diagnostics and therapeutics of brain disorders.

I. Introduction

Photonics is consistently expanding its reach in a wide variety of fields. As an example, biophotonic related applications are continuously evolving thus offering new possibilities to improve our understanding of living organisms. The disruption caused by photonics in medicine is perhaps only comparable to that observed in optical communications, two fields that have greatly evolved changing our everyday life. Current efforts in medical applications aim at combining technologies in order to provide multifunctional capabilities: theranostics and optogenetics, for instance, combine several photonic technologies in order to provide exceptional tools for diagnostics and therapeutics.

Biomedical applications of photonics rely mostly on the optical features of a specific tissue. Light sources are selected trying to optimize the absorption and/or scattering in order to reach specific regions or organs within the human body. As an example, the so-called therapeutic window (600 nm to 1300 nm) allows for significant penetration of light owing to the weak optical absorption of tissue components. Devices such as oximeters and imaging techniques such as optical coherence tomography (OCT), for instance, have been developed within this spectral range. In some cases, however, procedures for theranostics require deeper penetration of light: drugs for photodynamic therapy, or proteins such as opsins commonly used in optogenetics, are activated with light. Increased light penetration would certainly allow for extending the reach of these techniques to organs such as the brain, whose optical access is limited by the highly scattering nature of the cranial bone. In this article, we describe our ongoing research efforts aimed at developing a platform to provide optical access to brain tissue over a wide wavelength range. This "Window to the Brain" (WttB) is expected to grant an effective means to facilitate the diagnosis and treatment of neurological disorders using laser-based techniques.

An increase in optical transparency of the cranial bone is relevant for applications requiring recurring access to the brain tissue. The techniques proposed thus far involve cranial thinning and glass implants that may compromise the mechanical features needed for brain protection. Our approach for the WttB platform, depicted schematically in Fig. 1, is based on a novel transparent nanocrystalline Yttria-stabilized zirconia (YSZ), providing adequate toughness and biocompatibility to be used as a cranial implant [1]. In the next sections, we expose some of the relevant features of this material, as well as some of the research topics related to photonics that are being explored to demonstrate the new capabilities that this window may offer to perform optical theranostics procedures in the brain.

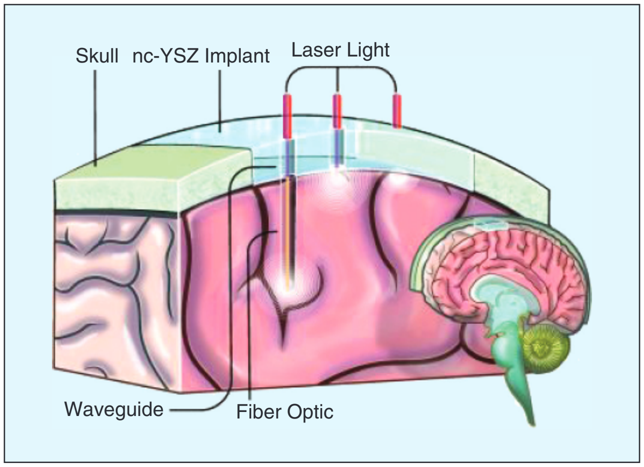


Fig 1. Conceptual scheme of the "Windows to the Brain" (WttB) platform.

II. A Multipurpose Window: Multidisciplinary and Binational Research Effort

The WttB platform is evolving through joint collaborative efforts from the United States and Mexico. Six research groups from the University of California and three from three different Mexican institutions (CICESE, INAOE and IIM-UNAM) have converged in a multidisciplinary group covering the relevant research topics required to develop this novel concept of a transparent cranial implant. The main goal driving this effort is to enable light and other types of electromagnetic radiation to reach the brain tissue, in order to provide a novel platform for new studies aimed at understanding how the brain works and communicates. Hence, this WttB platform must be capable to provide suitable optical, mechanical and thermal properties for performing these tasks using different theranostics tools. Research topics pursued in the project include processing and synthesis of micro/nanostructured materials, biomedical optics including laser-tissue interactions and bioheat transfer, and MEMS-based biomedical devices. Other photonics related research, some of which is covered in this article, focuses on optimizing light coupling and harvesting through the window. Finally, the research group also includes a strong biomedical component that will allow validating the use of the implants, as well as the photonic tools and techniques, in mice models.

III. Nanocrystalline Yttria-Stabilzed Zirconia (YSZ): Optical Features and Biocompatibility

Transparent ceramics have been of interest for a wide range of applications. Polycrystalline YSZ in particular has shown to be one of the most versatile ceramic materials owing to its biocompatibility, high hardness and toughness, although for optics related applications, its opacity has been typically a constraint. Using novel processing techniques, the optical scattering can be conveniently reduced thus yielding a highly transparent ceramic.

A. Optical Transparency

The optical properties of ceramics are related to the crystal structure, and more specifically, to the grain boundaries and porosity. A window is fabricated following a densification process of nanocrystalline YSZ powder. Upon adjusting the processing parameters, the optical transparency of the resulting densified ceramic can be modified [2]. For the WttB cranial implants, YSZ processing involves the use of high pressure and high electrical current in order to increase the sintering temperatures. Among other advantages, this procedure allows to retain the nanometric scale of the grains as well as to reduce the porosity [2], [3]. These features are directly related to the scattering properties of the YSZ ceramic and can be readily tuned to yield adequate transparency. After processing, the densified samples are polished, annealed and cut into proper dimensions.

Characterization of the optical properties of the YZS samples has shown that scattering is effectively reduced upon adjusting the sintering temperatures of the precursor powders [2]. Most of the opacity has shown to be related to absorption within wavelength ranges typically observed in reduced YSZ crystals [3]. Research is still underway to optimize the processing parameters to reduce absorption effects, which can be altered upon adjustments on the processing time. So far, the YSZ windows have shown to have a transmittance near to 60% within the wavelength range of the therapeutic window (see Fig. 2). As for the refractive index, it has been measured to be typically between 2.13 and 2.15 within a wavelength range from 300 to 600 nm.

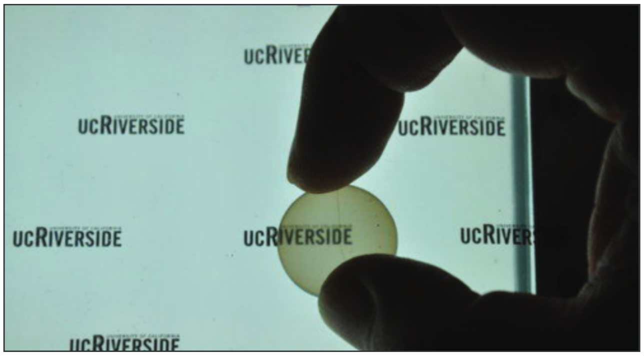


Fig 2. YSZ sample: the material offers adequate mechanical properties and transparency for developing cranial implants that may grant access to the brain tissue for optical theranostics.

B. Cranial Implants and Biocompatibility

An early demonstration of the potential of the YSZ as an enabling platform for brain theranostics was performed in mice [3]. The ceramic implant was fixed on top of craniectomies performed on one side of the skull while keeping the other side intact to serve as control. Using OCT as a representative optical imaging modality, images were acquired from both sides of the skull, i.e., through the native cranium and through the YSZ implant. Results showed that the implant indeed provides enhanced transparency, yielding images of brain areas otherwise imperceptible by OCT [3]. As explained in the following section, these promising results have driven efforts to explore the use of the implants with other optical techniques.

Although YSZ has shown to have good biocompatibility when used for dental and orthopedic applications, cranial implants evidently impose different biological challenges. Undergoing efforts in this direction include evaluation of the long-term biological response to this material, as well as potential reduction in transparency of the YSZ due to bone regrowth over the implant. Experiments in this direction are being performed with mice following approved protocols, and involving evaluation of OCT image degradation with time.

IV. A Window for Photonics

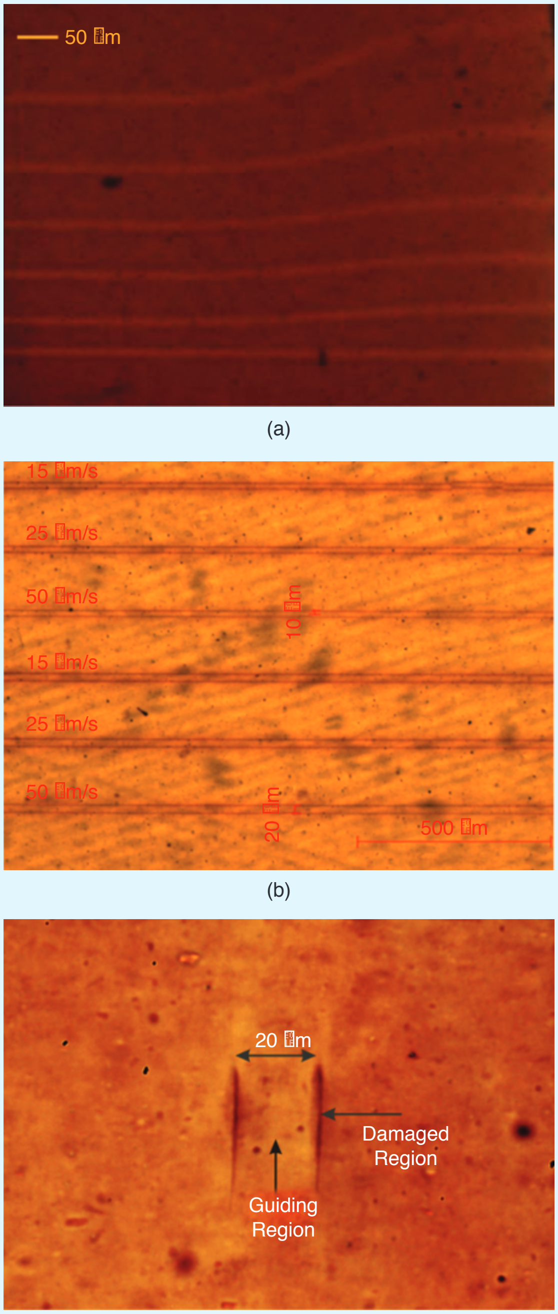
Clearly, gaining optical access to the brain tissue will extend the possibilities for using photonics tools. In this section, we present some of the approaches that we are pursuing to increase and control light delivery through the window.

A. Waveguides and Optical Fiber Coupling

Although the transparency of the material already provides optical access over a wide wavelength range, some applications may require for light to be delivered in a more concentrated fashion. Improved and/or directional light coupling through the window is being explored in two ways: direct waveguide femtosecond laser fabrication on the YSZ, and optical fiber coupling.

Waveguide-like structures are possible to fabricate in the YSZ through direct laser writing. Using femtosecond laser pulses, the optical properties of the YSZ samples can be readily modified thereby yielding waveguide-like structures [4]. We have demonstrated two types of structure in the YSZ polycrystalline ceramic, type I waveguides in which the guiding region corresponds to the laser scanned region, and type II waveguides, in which light is confined by a pair of parallel tracks produced by laser irradiation. While for type I waveguides the material increases its refractive index within the laser exposed region (Fig 3a), the confinement tracks in type II waveguides show a reduction in the refractive index (Fig 3b, 3c). The size of these structures depends on the laser parameters such as fluence per pulse and number of scans.

In contrast to conventional ceramics, the energy per pulse required to achieve these structures in the nanocrystalline YSZ is extremely low (around 5 nJ). The mechanisms involved in waveguide formation are still under examination, but so far the



(a)

(b)

(c)

Fig 3. Waveguide-like structures fabricated on samples of nanocrystalline YSZ ceramic by direct laser writing: (a) type I waveguides, (b) type II waveguides; (c) detail of type II waveguide showing the light confinement tracks produced with laser irradiation.

observed changes in the samples have been associated to the concentration of oxygen vacancies. Thus, processing parameters such as annealing time of the YSZ are thought to play a role in waveguide fabrication [4]. These preliminary results have provided evidence that the refractive index of the samples can be readily changed under laser irradiation. Efforts are underway to quantify this increase in refractive index and hence produce more elaborated waveguide arrays such as diffractive structures. Improved understanding of the mechanisms involved in waveguide formation will certainly provide new guidelines that may lead to fabricate complex waveguide structures in 3-D. Aside from improved light coupling through the ceramic implant, these capabilities may enable the design and realization of optical sensing structures within the WttB.

Light delivery to specific areas of the brain may be attained through optical fibers. Coupling of fibers to the window is being explored following different approaches. Given the nature of the implants, zirconia ferules such as those regularly used for optical fiber connectors should provide good compatibility for direct connection to the YSZ. Albeit requiring elaborated mechanical arrangements, laser soldering of zirconia ferules to the YSZ may represent a viable option. However, the index mismatch between standard fibers and the ceramic material has to be accounted for as a potential source for light reflection that may be detrimental for some applications.

Current tools available for optogenetics are also sought to be compatible and easy to adapt to the WttB implants [5]. Efforts in this direction include post processing of the YSZ to host the ferules and fiber arrangements typically used for light delivery. Increased reach of laser light to targeted opsins could be achieved upon attaching the zirconia ferules within the implant thereby providing a direct interface for optogenetic procedures. Micromachining techniques may offer a possible option for fitting the fiber ferules within the YSZ samples, although care must be taken to avoid compromising the mechanical properties of the material.

B. Fiber Optic Devices for Therapeutic Applications

Efficient coupling of fiber optics to the cranial implants will also provide a means to incorporate fiber-based devices. This is relevant among other things for therapeutic applications. As an example, we are currently exploring the use of optical fiber microheaters as photothermal tools for hyperthermia applications. The microheaters are based on gold nanolayers deposited on the tip of standard single-mode fibers [6]. A laser diode coupled to the opposite end of the fiber is used to generate the desired photothermal effect at the gold-coated fiber end. Simultaneously, we are also developing fiber optic temperature sensors that could either operate as stand-alone devices, or as part of a fiber probe that includes the microheater. The sensors are based on fluorescence thermometry, and the devices are fabricated using rare-earth (RE) compounds embedded in a biocompatible polymer matrix (PDMS). As shown in Fig. 4, the RE-PDMS composite is attached and cured on the tip of a dual-fiber arrangement. The RE ions are excited with a NIR laser diode to produce fluorescence bands within the visible spectral range and this upconversion process is temperature dependent. Hence, spectral analysis of the fluorescence captured by one of the fibers can be used for temperature monitoring. Joining both, the fiber microheaters and the temperature sensors should provide a novel way to achieve a controlled temperature set point on demand and in a highly localized manner.

Coupling fiber optic devices through the YSZ implants can certainly provide an effective means to extend theranostics capabilities. Parameters such as pressure and temperature, typically used for monitoring brain recovery after traumatisms and other conditions, could be readily monitored with fiber sensor technology through a ferule conveniently located in the WttB. Similarly, optogenetics tools, such as the recently demonstrated all-fiber optrodes [7], could also be allocated in the implants housing the zirconia ferules. Developing a practical and versatile multitasking fiber optic interface for the implants is therefore an important goal for the WttB platform.

C. Diagnosis and Therapeutics with Photonic Tools

The availability of a transparent window for brain studies provides an excellent opportunity for extending the reach of optical theranostics tools. Optical imaging technology is perhaps the most natural candidate to be exploited for improved diagnosis of brain disorders. Aside from OCT, which has already shown to increase its resolution through the window, laser speckle imaging (LSI) is being explored as a means for tissue analysis and blood flow monitoring. LSI is a well-known technique used to monitor neurovascular and tissue metabolic activities at high spatiotemporal resolutions over a relatively large field of view. We have been working on different computational techniques to improve the visualization of deep blood vessels up to ~1000 mm [8]. Additionally, the highly scattering nature of the brain tissue could be partially reduced through wavefront correction of the incoming beam. This can be achieved by means of a spatial light modulator allowing, for example, focusing a beam into deeper brain regions even after travelling through the tissue. Enhanced resolution in optical imaging will indeed provide a better insight of ailments such as cerebral edema or others requiring chronic monitoring.

Further information of the brain tissue may be obtained with other techniques such as Müeller matrix imaging [9]. This polarization sensitive technique is capable to provide information about physical parameters of scattering media such as tissue. For the WttB platform, a reflection scheme for imaging is being developed in order to obtain polarization-encoded information through the YSZ implant. Brain tissue features such as inflammation or tissue differentiation may be identified through birefringence and retardance analysis.

Therapeutics with optics typically involves light activated processes. Evidently, the advent of transparent ceramic implants promise a new test bed for both, exogenous and endogenous optical procedures. Although the reach of light activated drugs to the brain tissue may still be challenging, the availability of a window for light delivery offers a new incentive for pursuing more efforts in this direction. As an example, techniques such as photodynamic therapy may extend their reach for brain tumor related treatments [10]. So far, we have shown that PDT can effectively be used with different photosensitizers for treating dermatophyte fungus, bacteria, as well as breast cancer [11]. Research on biological activity triggered by light, such as ionic channel activation at the cellular level, may be also explored through the WttB platform. Finally, as mentioned earlier, an interface for optogenetics and the implants is also being considered in order to facilitate light delivery for these procedures.

D. Laser-Assisted Antiseptics

Antiseptic methods are important in all medical related procedures. As part of the development of the WttB platform, we are exploring the use of laser-assisted methods for bacterial and microorganisms control. This approach has been extensively studied for dental related applications using near-infrared (NIR) lasers yielding good results for controlling bacterial growth. Cranial surgery or trauma commonly leads to infectious processes involving bacterial growth, posing a challenge for treatment owing to the poor penetration of antimicrobial agents to this tissue. For cranial implant infection in particular, the implant needs to be removed and replaced thus adding inconvenience and cost to an already delicate procedure. A non-contact, light mediated process through the window for antiseptics would therefore be useful for the WttB platform.

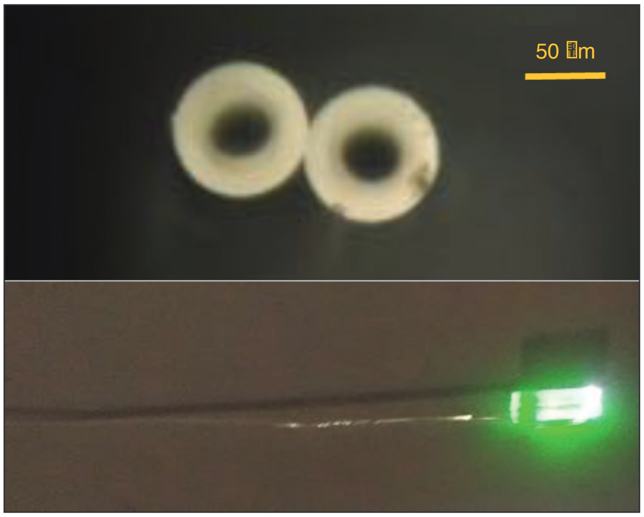


Fig 4. Fiber optic temperature sensor with rare-earth compounds embedded in a polymer matrix (PDMS). Temperature measurements are obtained monitoring the fluorescent intensity (green light) of the polymer compound.

Preliminary efforts for laser-assisted control of bacterial growth through YSZ ceramics have shown promising results [12]. Using a NIR laser diode in *in vitro* experiments, we have observed growth inhibition of *Escherichia coli* (*E. coli*), commonly appearing in some forms of meningitis after cranial surgery or trauma. Laser irradiation performed through YSZ showed to disrupt *E. coli* biofilm formation, thereby providing evidence of the potential for laser-assisted procedures through the implant. Recently, we have also observed mitigation of *E. coli* growth using femtosecond laser pulses of ultra low energy (<5 nJ) with MHz repetition rates. Interestingly, the process does not seem to be related to thermal effects, as evidenced by thermal imaging measurements during laser irradiation (Fig. 5). Bacterial inactivation monitoring has shown that damage occurs after a characteristic irradiance threshold, suggesting that nonlinear optical effects may play a role in this process. Research in this direction is therefore aimed at exploring the role of nonlinear optical effects (e.g. nonlinear absorption, multi-photon dielectric breakdown) in bacterial damage.

It is important to identify the mechanisms involved in the inhibition of bacterial growth with laser light mostly to prevent any secondary effects that may occur during this process. Photochemical and photothermal effects are being considered as the main contributors to the results observed so far. Ideally, a purely photochemical effect would be desired because this will prevent increasing the temperature in the vicinity of the tissue.

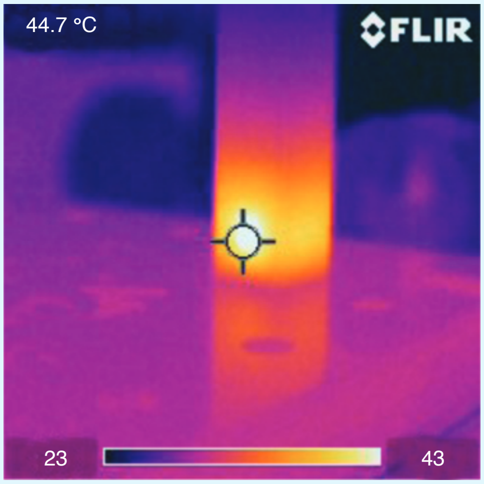


Fig 5. Typical thermal image of a bacteria solution in a quartz cuvette under laser irradiation. In spite of long exposure times (in this case one hour), the maximum temperature in the solution barely reaches 45 °C.

The use of optical methods for monitoring bacterial growth is also being explored aiming at developing an all-optical tool for antiseptics through the WttB platform.

V. Conclusions

Biomedical related applications of photonics are consistently extending their reach to increase our knowledge of living organisms. The challenges posed by the complexity of biological systems demand joint efforts on multidisciplinary research, and photonic tools are undoubtedly valuable. Our ongoing research, focusing on developing a platform for brain related studies, ties activities related to materials science, biomedicine and photonics. We expect that this collaborative effort will provide a novel means to obtain useful information to increase our understanding of the brain and its ailments. More importantly, the WttB platform should provide an effective way to increase the possibilities for performing theranostics in the brain. Photonics plays a fundamental role to achieve this task, offering several optical techniques and devices that could be interfaced through the window.

Acknowledgments

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Correction

In the December 2017 Issue Research Highlights an author's name was missing. The online version has now been corrected to include George Papastergiou of Optronics Technologies SA, Athens, Greece.