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The Emergence of Medical Laser based Diagnostics to Battle against Complex Diseases

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Abstract

Lately, we have witnessed an explosive growth of innovative lasers and optical devices for clinical diagnostics and therapeutics including assessing human health and treating complex diseases. It is believed that light and optical techniques can have profound impacts on modern medicine. To this end, advances in medical lasers enabled biomedical optics have resulted in sophisticated technologies that integrate several other technologies including photonics with nanotechnology, biomaterials and genetic engineering, to name a few. Especially, novel biomedical laser applications based on new laser types or novel energy delivery systems could increase the usable range of laser-tissue interactions, and thus improve target-oriented, high precision application of laser radiation in clinical practice. Here, we have presented a perspective analysis of recent demonstrations of medical lasers for complex diagnostics including clinical diagnostics applications.

Keywords: Medical laser, diagnostics, Alzheimer's disease, skin cancer, pathogens

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DOI: https://doi.org/10.37756/bk.22.4.4.1
Article type: *Perspective*
Received: *March 2, 2022*
Revised: *March 20, 2022*
Accepted: *March 22, 2022*

Please cite this article as: *Singh PK, The Emergence of Medical Laser based Diagnostics to Battle against Complex Diseases, Biotechnol. kiosk, Vol 4, Issue 4, PP: 1-8 (2022); DOI: https://doi.org/10.37756/bk.22.4.4.1.*

Introduction

Medical laser applications have manifold dimensions that involve advanced technologies. These applications are aimed to meet current challenges in clinical diagnostics and therapeutics to battle against complex diseases such as blood borne pathogens, skin cancer and cardiovascular and neurodegenerative diseases, to name a few. Medical laser based diagnostic technologies are capable of addressing a wide range of health care issues that could have significant impact in the future on large sectors of the population. With respect to recent research activities and ongoing innovative developments, researchers have shown short- to mid-term improvements of both clinical diagnostics and therapeutic procedures as well as for the extension of the applicability of established techniques for new medical indications. For example, it has been shown that novel biomedical laser applications based on new laser types or innovative energy delivery systems could increase the usable range of laser-tissue interactions that could improve target-oriented, high precision application of laser radiation in clinical practice.

Studies have indicated that these new energy delivery techniques together with innovative key medical techniques that are now at the translational stage into the clinics could pave the way to many future breakthroughs in medical diagnostics [1-3-4].

With respect to clinical applications, researchers have shown the promise of optical biopsy and non-destructive diagnosis techniques. However, these techniques still have to overcome challenges to be recognized as standard techniques for commercial applications. While histopathology of excised tissue samples is still considered the gold standard for diagnosis, latest research has focused on developing new non-invasive laser and photonics-based diagnostic techniques. A significant focus has been on oncology to develop laser-based techniques that rely on the physical and biochemical changes that precede or mirror malignant changes within tissue and involve simple optical tissue interrogation techniques. Several studies have shown their accuracy in terms of sensitivity and specificity that have demonstrated the potential for a cost-effective, real-time, in-situ diagnosis for specific diseases and conditions [5-6-7-8- 9-10-11-12-13].

Here, we will take a look at some of the notable applications of laser based diagnostic tools that have been employed to combat complex medical conditions.

Detection of Pathogens in Blood Borne Infections

It is a known fact that the ability to detect and identify pathogens in blood borne infections is very important for either patient treatment/monitoring and also to make sure the safety of the donor blood supply. The existing diagnostic methodology for the detection of an infection and the identification of the responsible organism typically requires up to 72 hours depending on the pathogen. This is also dependent on the use of highly skilled personnel along with complex sample preparation. Additionally, it often requires transport of a blood sample to a microbiology laboratory for analysis. To overcome these challenges, the ability to rapidly diagnose blood borne infections on-site that does not require simple sample preparation and also highly skilled personnel is currently needed. It is believed that rapid detection would greatly enhance the ability to identify, contain, and treat blood borne infections. This can also greatly reduce the time needed to screen donated blood for infections. Moreover, the development of a blood diagnostic with these capabilities is considered a significant advancement that can enable rapid screening of patients for infections and treatments immediately.

To this end, researchers have demonstrated point-of-care diagnostic instrumentation that is based on the analysis of spectra collected from a series of laser sparks formed on a blood sample. The methodology is known as Laser-Induced Breakdown Spectroscopy (LIBS), which is an established spectrochemical analysis technique. In this process, a laser pulse is used to simultaneously vaporize a small sample mass and excite the resulting atoms to emit light via formation of a hot plasma on the sample surface. Subsequently, light from the plasma is collected, spectrally resolved and finally recorded. Further, the instrument has been shown to be programmable for multiplex detection. This allows the programming to be expanded as new algorithms are developed to detect additional infections. Therefore, it is thought that a laser-based approach can achieve sensitive, multiplex detection with minimal sample preparation and provide rapid results. These important properties together with the flexibility to add new agent detection by simply adjusting the detection programming make it a promising tool for clinical diagnosis [14].

The recent studies have focused on clinical diagnostics of newly emerging agents and to screen simultaneously for multiple infectious agents. To this end, laser-based diagnostic techniques have been demonstrated to rapidly detect the presence of parasites, bacteria and viruses in human blood. For example, researchers have successfully demonstrated differentiation of blood spiked with viruses, bacteria, or protozoan parasites. This was achieved at clinically relevant levels using six blood types (O+, O-, AB+, A+, A-, B+) from different individuals with blood samples. Spiked samples were shown to be useful to detect pathogens at low concentrations in human blood using multivariate methods on carefully controlled samples. This showed the ability to detect blood samples spiked with the bacteria *S. aureus* and *Yersinia pseudotuberculosis* (*Y. pseudotuberculosis*), the parasite *Trypanosoma cruzi* (*T. cruzi*) and the Human Immunodeficiency Virus (HIV-1) by analysis of LIBS spectra [14].

Diagnosis of Alzheimer's disease using Laser-Induced Breakdown Spectroscopy and Machine Learning

Alzheimer's disease (AD) is known as a progressive incurable neurodegenerative disease and considered a major health condition in aging population worldwide. The magnitude of devastation caused by AD can be understood by an estimate that the number of AD cases in the US alone will exceed 20 million by the year 2050. It is believed that the related healthcare costs will reach $1 trillion. It is widely recognized that an early diagnosis that allows for non-invasive cost-effective tests for AD along with clear discrimination of AD from other dementias is pivotal for an efficient AD management. This is vital for the success of clinical trials of drug candidates. Recently, researchers proposed a minimally invasive approach to medical diagnosis based on LIBS liquid biopsy technique. They employed easily harvested biological fluids, such as blood, urine or saliva that were deposited and dried on solid substrates prior to laser irradiation (Figure 1) [15].

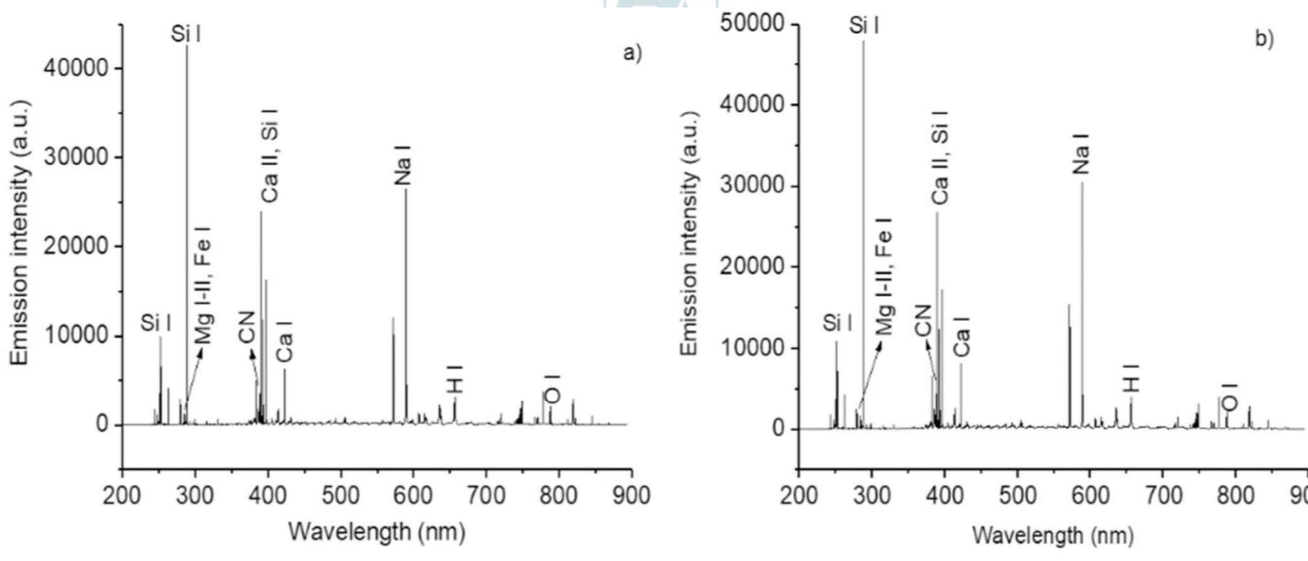

Figure 1: *(a-b): LIBS spectra of the blood plasma of an AD patient are shown. The plasma is deposited on a Si substrate [Source: Spectrochim Acta Part B Atomic Spectroscopy (2020)].*

In this study, researchers proposed the combined use of LIBS and machine learning for the diagnosis of AD using biomedical fluids. They analyzed micro-drops of plasma from a cohort of

AD patients and HC and focused on distinguishing the two classes with a data analysis approach based on the use of LIBS difference spectra. This study paves the way to further investigations on the potential of the combined use of LIBS and multivariate statistical approaches to analyze rapidly and relatively simply a large number of biomedical samples for the diagnosis of asymptomatic diseases [15].

Optical Coherence Tomography and Confocal Laser Scanning Microscopy: Non-Invasive Imaging for in-vivo Analysis to Combat Skin Cancer

Optical Coherence Tomography (OCT) is considered a non-invasive imaging technique with an NIR laser source. OCT is employed for in-vivo skin analysis that offers real-time, cross-sectional evaluations of the skin. In the OCT process, the backscattered light from a given depth in the tissue is recombined with a static reference signal. This is followed by an interference occurs in the event of matching of both path lengths within the so-called coherence length of the light source. This enables create both two-dimensional (2D) and three-dimensional (3D) images (Figure 2) [16].

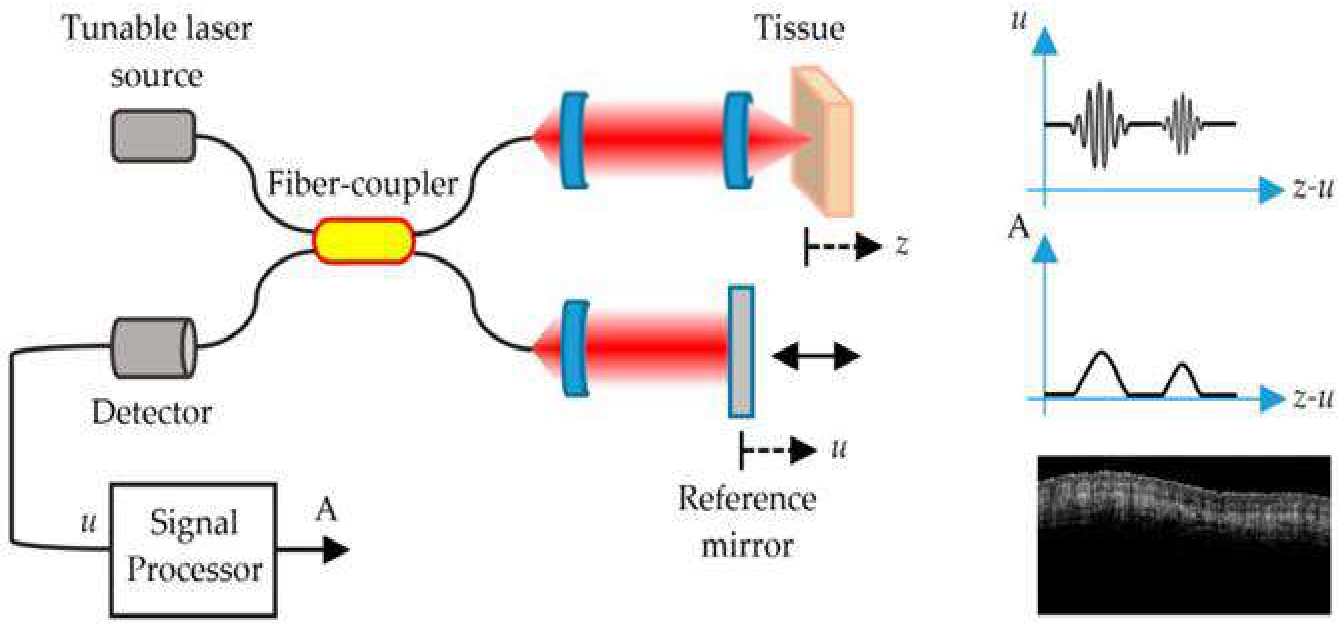

Figure 2: *Schematic illustration of a swept source (SS) OCT imaging system (μ is the reference signal and A is the interference signal producing the image of the different layers of the skin) [Source: Sensors (Basel) (2021)].*

OCT angiography (OCTA) is usually employed for the visualization of vascular patterns in the skin angiogenesis (a sign of growth and spread of cancers) that is considered helpful in improving diagnostic accuracy [17]. Another emerging technique is the confocal laser scanning microscopy (CLSM), which is a promising in-vivo and ex-vivo technique for diagnostics in clinical settings. CLSM enables a quasi-histologic view of a given tissue and that does not require a biopsy. The technique is based on refractive index of cell structures that serve as endogenous chromophores, which allows reaching a depth of exploration of 200 μm [18]. In a recent study, researchers demonstrated in-vivo CLSM in reflectance and fluorescent mode for real-time pathological examination of freshly excised specimens for diagnostic purposes. This allowed for the evaluation of margin clearance after excision in Mohs surgery (Figure 3) [18].

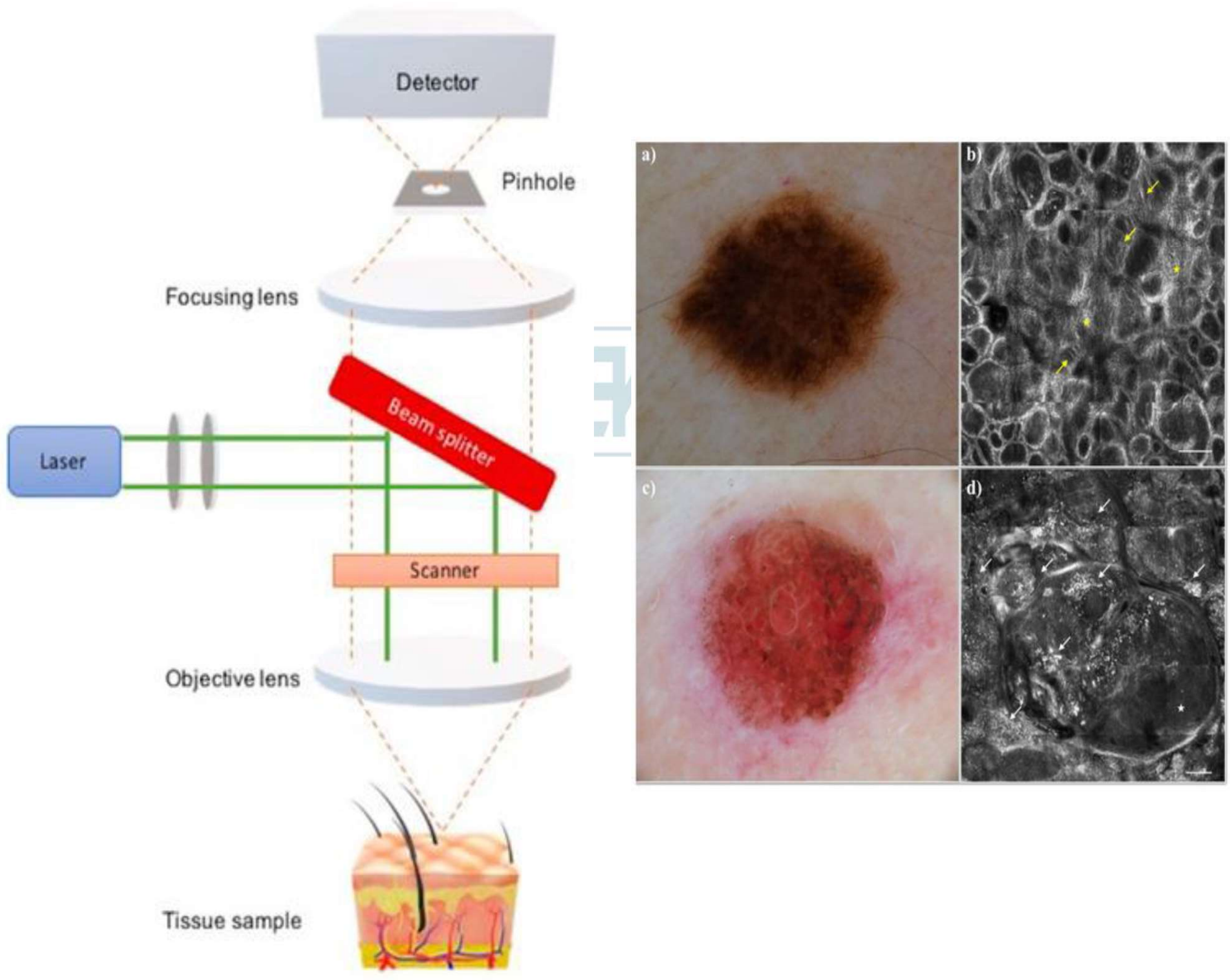

Figure 3: *(Left) Schematic illustration of optical principles of confocal laser scanning microscopy. (Right) (a-d) Dermoscopy of a melanoma in-situ is shown that include in-vivo reflectance confocal microscopy showing several pagetoid cells (yellow stars) at the epidermal level and atypical cells at dermo-epidermal junction (yellow arrows) and a typical melanocyte (white arrows) [Source: Appl. Sci. (2021)].*

Conclusion

Laser based diagnostic tools have proven to be very effective in the early detection and intervention in several complex diseases. Several techniques have been shown in recent studies that offer hope to combat a number of diseases that include blood borne pathogens, neurodegenerative diseases and skin cancer, to name a few. We anticipate further development of laser diagnosis in the near future for non-invasive and early detection of diseases for timely intervention and cure.

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