Biophotonic imaging – the medical needs in otolaryngology, head and neck surgery

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Introduction

Modern otolaryngology and head and neck surgery are medical disciplines that were emerged to a great extent by the achievements of modern optics and microscope developments. The dominating optical technique for endoscopic and microscopic diagnostics still is the examination with white light. There are promising biophotonic techniques already introduced to the field or on the stage of introduction that will help to improve otorhinolaryngolic disease discrimination, classification, and early diagnostics. The techniques will bring forward the field of optical biopsies and intraoperative biophotonic surgery guidance.

Methods

Since about 10 years our interdisciplinary and interfaculty team of physicists, chemists, computer scientists, physicians, and head and neck surgeons conducts research in the field of biophotonic diagnostic in the field of otolaryngology and head and neck surgery. Main techniques used are hyperspectral imaging, optic coherence tomography (OCT), laser endomicroscopy (CLE), near-infrared (NIR) imaging, non-linear optic imaging (CARS, SHG, TPEF), Raman, and multispectral optoacoustic tomography, i.e. marker-free as well as fluorescence marker-based technologies. The presentation will focus on and summarize in a major field of medical needs: better intraoperative tumor border discrimination.

Results

The combination of biophotonic diagnostics with deep learning algorithms was necessary to realize fast tools for intraoperative biophotonic-guided surgery. Ex vivo, on the tissue samples, biophotonic diagnostics have already now a high specificity and sensisivitiy to allow optic biopsies. Direct analysis of interoperative non-processed samples is realized at the moment. In vivo, the available licensed methods are so far too slow for automated tissue classification and very promising photonic methods are not licensed yet.

Conclusion

Combining multiple photonic imaging techniques could allow for new, noninvasive approaches to tumor detection and assessment, meeting important need of otolaryngology, head and neck surgery. All these scenarios are also important prerequisites to make the step from passive to active biophotonic-guided robotic surgery.

Intraoperative diagnosis, monitoring and therapy using spectroscopic multi-contrast imaging

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Introduction

In tumor surgery, there is a great need for new technologies that are able to localize the tumor exactly in order to remove it as complete as possible and that allow for a reliable tumor typing and grading in order to initiate an individual therapy plan tailored to the patient as quickly as possible. Thus, new diagnostic approaches, which can be applied intraoperatively, i.e. in-vivo or near in-vivo (e.g. as frozen section analysis approach) are required.

Methods

Multimodal nonlinear imaging, using different methods such as coherent Raman scattering (CARS, SRS), two-photon excited autofluorescence (TPEF), multi-photon excited fluorescence lifetime imaging (MPE-FLIM) and second harmonic generation (SHG), represents a powerful tool for the label-free characterization of the molecular composition of biological tissue.

Results

Here, we highlight the potential of multimodal nonlinear imaging to reliably assess tumor tissue and the success of an operation directly in the operating theatre. We will introduce novel multimodal spectroscopic instrumentation (like e.g. clinically usable non-linear multimodal microscopes or endospectroscopic probes) for precise surgical guidance and intraoperative histopathological examination of tissue under in-vivo or near in-vivo conditions. Besides innovative photonic technologies, the presentation will also introduce innovative image evaluation algorithms for the translation of multimodal images into quantitative diagnostic markers. Furthermore, it will be shown that the presented multimodal approaches can be combined with laser tissue ablation for tissue specific laser surgery and for therapy monitoring, i.e. visualization of cold atmospheric plasma (CAP)-induced changes in tissue.

Conclusion

The presented multimodal imaging approach offers an unique potential for intraoperative tumor diagnosis and therapy.

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Cold plasma therapy systems for medical application

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Introduction

Plasma medicine is an innovative research field combining plasma physics, life science and clinical medicine. It is mainly focused on the application cold atmospheric plasma (CAP) in therapeutic settings. Current medical applications are realized in treatment of wounds and skin diseases. CE certified medical devices are on the market. Dominating action mechanisms being based on redox-controlled cellular processes are understood in general. Safety of CAP application with specific regard to genotoxicity was proven repeatedly. Besides the opening of new application fields e.g. in cancer treatment, present research is focused on optimization of CAP application by on-site monitoring and control of both plasma and target characteristics during treatment.

Methods

To monitor plasma effects on the treated target, e.g. a wound surface, spectroscopic techniques like hyperspectral imaging or Raman spectroscopy can be used. Electrical measurements of voltage and current as well as optical emission spectroscopy are useful tools to monitor changes of plasma characteristics during treatment.

Results

By hyperspectral imaging techniques short-term physiological effects, especially hemodynamic parameters, on a plasma-treated wound can be visualized in a contact-free manner. Imaging methods based on Raman spectroscopy and other techniques are useful to visualize biochemical effects at the plasma-tissue interface. By direct monitoring of plasma characteristics and device performance parameters, the influence on plasma parameters by specific characteristics of the target and its changes, e.g. its electrical conductivity, can be determined.

Conclusion

Currently, CAP treatments take place without any possibility to register if there was sufficient plasma-tissue interaction to realize the intended medical effect in a short-term manner. Additionally, any changes of plasma parameters by feedback effects of the target characteristics are not taken into account yet. Combination of plasma-orientated and target-orientated monitoring tools with a CAP-based medical device will lead to an integrated CAP therapy system. Bringing together all the different monitored signals in a data processing and control unit, a direct feedback regulation of plasma treatment should be the result. With such a compact system for plasma treatment, monitoring and control, the step from medical CAP devices to integrated CAP therapy systems will be realized.

Living Therapeutic Materials - Hydrogel-confined Bacteria for Smart Drug Delivery

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Introduction

Synthetic biology and metabolic engineering have facilitated programming of microbes with intricate genetic functionalities such as of sensing external factors, performing logic functions and producing a wide range of industrially-relevant compounds. As a consequence, such microbes have been developed as biosensors and these sensory functions have been combined with their drug-production capabilities to engineer them as live biotherapeutic agents. Such bacteria have the capability of in situ drug production and release at a disease site in a manner that can be regulated either manually by external stimuli or automatically by disease-specific markers. This is seen as a highly cost-effective therapeutic bioprocess, since it eliminates the need to externally produce, extract, purify, package and store the drugs before their use. However, applicability of such therapies is limited by the fact that bacteria need to colonize the disease site and may cause tissue damage or microbial dysbiosis in return. To overcome this issue, we are exploring biocompatible hydrogel-based strategies to securely confine bacteria in a functional manner such that their smart therapeutic activity is retained but physical contact with tissues is prevented.

Methods

Agarose, PEGDA and pluronic-based hydrogels were used for bacterial encapsulation and varied in their composition to obtain gels with different material properties. Mechanical characterizations were performed using a rheometer and bacterial growth/viability studies were followed through phase-contrast and fluorescence microscopy. E. coli were optogenetically engieneered to produce both protein- and small-molecule-based drugs in a light-regulated manner. Analysis of drug production was followed spectrophotometrically. 3D biopriting was performed with bacteria-loaded hydrogels to obtain living therapeutic materials of desired dimensions and geometries.

Results

Appropriate strategies were developed to encapsulate the bacteria within the different types of hydrgoels while maintaining their functionality and preventing their escape into the external medium. Correlations were identified between mechanical properties of the gels and bacterial growth/viability that in turn led to tunability of drug release kinetics. Light-regulated drug release provided the possibility of remotely controlling drug release in a locally confined and dosable manner. The bacterial-hydrogels maintained viability and drug-releasing functionality for several weeks to months. 3D bioprinting of these living therapeutic materials allowed the possibility to customize their dimensions and geometries to suit different potential therapeutic applications.

Conclusion

Living therapeutic materials represent a unique approach to smart drug delivery with the advantages of prolonged activity, in situ drug production, complex stimuli-responsive capabilities and cost-effectiveness. Our work lays the foundation for developing such materials towards clinical applications.