1. Introduction

Optoacoustic Imaging (OAI), also known as Photoacoustic Imaging (PAI), is a method of imaging that utilizes the generation of mechanical waves due to light absorption by chromophores within tissue (Fig. 1) [1]. More specifically, the terminology of OAI is used to describe the light-induced sound phenomena that occurs when the excitation light is within the visible and near-infrared portion of the electromagnetic spectrum [2]. If the excitation energy is within the radio-frequency or microwave region, the imaging technique is instead referred to as Thermovacoustic Imaging. These two mechanisms of signal generation have been exploited for a wide range of applications over the past several decades, from gas spectroscopy [3], to thin film characterization [4], to studies of photosynthesis [5]. In 1982, Olsen published the first paper reporting successful 2D imaging with biomedical potential [2]. In the 1990s, optoacoustics began to be more seriously explored for applications in medical imaging due to advances in both laser light sources and acoustic detection equipment [6]; this was followed soon after by the first report of an in vivo imaging system in 1993 by Chen et al. [2].

The premise of using optoacoustics in medical imaging is straightforward. First, the tissue of interest is illuminated by a sufficiently short pulse of light, such that the pulse length satisfies both the thermal and stress confinement conditions [7]. This light is absorbed by specific components within the tissue, such as hemoglobin or lipids, generating a mechanical wave whose frequency is in the ultrasound regime. These signals can be detected by an ultrasound sensor, or array of ultrasound sensors, and the signals can be used to form an image with any of a variety of image reconstruction algorithms currently available in the literature [8]. The resulting contrast of the image is based upon the distribution of absorbed optical energy within the tissue, which is related to the wavelength of light used and the optical properties of the tissue under study [7].

The primary safety concern in OAI is the damage to tissue due to light exposure [9]. Most studies use the maximum permissible exposure (MPE) limits set forth by the American National Standards Institute (ANSI), which has written guidelines for the use of lasers in medicine [9,10]. The limits described by the ANSI define the MPE for a single, short pulse of laser light (1–100 ns pulse length) with a wavelength between 400–700 nm to be 20 mJ/cm², and 100 mJ/cm² for wavelengths between 700 and 1400 nm. The ANSI also provides MPEs for applications that used repeated pulsed light. Other safety concerns for OAI include damage to the eyes of patients and practitioners. This may be addressed using common safety controls for lasers, which includes appropriate eye protection and engineering controls such as curtains.

Because OAI relies upon the absorption of light for signal generation and the detection of ultrasound waves for signal acquisition, it presents several advantages over other medical imaging modalities, such as optical microscopy and ultrasound imaging. For example, typical high resolution, light-based imaging, such as optical microscopy or optical coherence tomography (OCT), have limited penetration depths in tissue due to the significant scattering of light within the tissue, making it...
difficult to clearly image fine structures beyond \( \sim 1\) mm \([6,11,12]\).
Ultrasound-based imaging systems, on the other hand, have a greater imaging depth than light-based systems, but are hampered in their ability to differentiate between soft tissue structures because of their similar mechanical properties. The modality relies on the acoustic mismatch between tissues to generate contrast, which is associated with their mechanical properties; soft tissues do not generate a substantial amount of acoustic differences \([13]\).
In contrast, OAI combines the excellence of structure differentiation of light-based imaging with the imaging depth of ultrasound-based imaging: generation of optoacoustic signals is dependent on light absorption, making it possible to target specific biological compounds, such as hemoglobin and lipids, depending on the wavelength used \([1]\).
The incident light, then, only needs to reach the target and be absorbed in order to generate the acoustic signal. Moreover, unlike light, ultrasound waves experience relatively little scattering in tissue, allowing for signals that are generated deep within the tissue to be reliably detected, pushing the OAI modality far beyond the limits of either light-based or ultrasound-based modalities \([14]\).

In addition to the aforementioned advantages, OAI is scalable in terms of the resolution at which it can image: it can be used for macroscopic (753,500\(\mu\)m) \([15,16]\), mesoscopic (4,530\(\mu\)m) \([17,18]\), and microscopic imaging (1550\(\mu\)m) \([19]\). Macroscopic imaging via the OAI modality, which is frequently accomplished using Optoacoustic Computed Tomography (OACT), is, for instance, capable of imaging entire organs \([20]\).
Optoacoustic Microscopy (OMI), on the other hand, can be used to image small sections of tissue, such as capillary beds and subcellular structures. This OAI method can be divided further into two classes based on how resolution is achieved: acoustic resolution (AR-OMI) and optical resolution (OR-OMI). In AR-OMI, the resolution of the system is determined by the acoustic detection components, whereas in OR-OMI, the resolution is determined by the properties of the excitation light. In order to capture the continuous scalability of OAI, so-called ‘switchable’ or ‘hybrid’ AR- and OR-OMI systems have been developed \([21,22]\).
These systems can employ either AR- or OR-OMI methods by simply adjusting some of their components, demonstrating the power of OAI scalability. Lastly, Optoacoustic Mesoscopy (OMe) fills the gap between OACT and OMI, and has recently emerged as a valuable addition to the OAI suite \([23–26]\). Different OAI methods relevant to hand-held platforms are discussed in detail in Section 2.
Hand-held optoacoustic imaging platforms are typically defined as platforms that contain either a ‘free’ imaging head, i.e., are not rigidly attached to some supporting structure and whose position is able to be manipulated by the user, or are connected to an articulated arm and easy to manipulate by the user. Fig. 2 shows the different OAI methods and the relationships among the methods.

As previously mentioned, specific targets can be singled out using different wavelengths for optoacoustic signal generation. This is known as multispectral or spectroscopic OAI and has been used to selectively image compounds such as oxy-/deoxygenated hemoglobin or lipids \([27,28]\).
In this technique, at least two separate wavelengths are used to interrogate the tissue, and the magnitude of the resulting optoacoustic response at each wavelength is used to determine the prevalence of the target of interest. This can become complicated, however, by the need to account for the wavelength-dependent nature of light propagation in tissue when analyzing the amplitude of optoacoustic signals that originate from a particular volume of tissue \([29]\). Multispectral or spectroscopic OAI can be used with all of the aforementioned OAI methods. For instance, spectroscopic OACT, often termed multispectral optoacoustic tomography (MSOT), has found much success in applications such as visualizing oxygen saturation in the vasculature around tumors, imaging tumors in breast tissue, visualizing sentinel lymph nodes (SLNs), and visualizing vasculature deep in tissues, among others \([30–39]\).
Additionally, spectroscopic OMe, often termed multispectral optoacoustic mesoscopy (MSOM), has been used for selectively imaging melanin and blood, as well as visualizing the structure of skin in patients with psoriasis \([18,40]\). Lastly, quantitative OAI, a technique that uses multispectral OAI, seeks to quantitatively determine the concentration of a target; Quantitative OAI has proven more challenging because the fluence must be accurately modeled throughout the tissue so that it may be accounted for during signal processing \([8]\). Interested readers are referred to references \([41]\) and \([42]\) to learn more about spectroscopic OAI methods.

There are several metrics for evaluating OAI platforms. The first three are the axial, lateral, and elevational resolutions, analogous to ultrasound imaging \([43–45]\). These describe the spatial resolution of the platform along the imaging axis (axial), perpendicular to the imaging axis on the image plane (lateral), and between image planes (elevational). Other metrics include temporal resolution, contrast, and sensitivity. Temporal resolution is a measurement of how quickly a platform can acquire and generate images; high temporal resolution platforms are critical for improving the utility of OAI and reducing image artifacts \([1,46]\). Contrast is typically measured as either the signal-to-noise ratio (SNR) or the contrast-to-noise ratio (CNR). SNR is defined as the average background signal over the standard deviation of the background signal \([47]\), whereas CNR is defined as the intensity of signal that arises from the region of interest minus the average noise, divided by the standard deviation of the background signal. Lastly, sensitivity describes the minimum concentration of a target compound that the platform can detect \([12]\).

Over the last two decades, OAI has been used in numerous studies, some of which we will list here to showcase its clinical applications. Common applications include imaging melanoma \([19,48–50]\), imaging vasculature in various organs to indicate the presence of tumors...
[49–52], studying the vasculature around tumors [15,53–56], studying brain activity [46,57–61], and imaging lymph nodes to study tumor metastasis [62,63]. Other applications include imaging the vasculature of the retina for diagnosing diabetic retinopathy [64], imaging intestinal inflammation due to Cronh’s disease [32], imaging whole bodies of small animals [65], and imaging lipid plaque in the aorta [66]. While no clinical OAI platforms are currently available commercially, there are several platforms undergoing clinical trials [8]. As these clinical trials finish, we should expect to see commercially-available, clinical OAI platforms emerge.

Since OAI imaging was first proposed and demonstrated, the OAI research community has significantly refined the technology that supports OAI methods. As described by Taruttis and Ntziachristos, OAI has evolved in six dimensions [29]. The first three were spatial dimensions, referring to 1D (A-line scans), 2D (B-line scans), and 3D (volumetric) imaging. The next dimensional advancement was time-resolved imaging, allowing researchers to study dynamic processes in real time. This was achieved in large part due to the implementation of parallel signal detection methods from sensor arrays. Later, as laser technology advanced, the fifth dimension was established: spectroscopic imaging. Newly developed laser systems that could rapidly output different wavelengths were used to provide real-time OAI that could, for instance, determine the relative concentration of different compounds via spectroscopy [29]. This technique was first demonstrated in a hand-held MSOT platform in 2013, producing 2D images of oxy-/deoxy-hemoglobin and melanin in human skin [67]. MSOT is a powerful technique that has greatly expanded the utility of OAI. The sixth and final dimension described was multi-scale imaging. This was realized recently at the benchtop level by Moothanchery and Pramanik (2017) [21], whose team developed a switchable acoustic resolution and optical resolution OMi (AR-OR-OMi) platform. Beyond these dimensions, OAI methods have benefited from technological advances such as GPU-accelerated image reconstruction [68], specially designed ultrasound arrays [69], and advances in laser repetition rate, all of which increased acceleration of image reconstruction [68], specially designed ultrasound arrays [69], and advances in laser repetition rate, all of which increased acceleration of image reconstruction [68], specially designed ultrasound arrays [69], and advances in laser repetition rate, all of which increased acceleration of image reconstruction [68], specially designed ultrasound arrays [69], and advances in laser repetition rate, all of which increased acceleration of image reconstruction [68].

In recent years, much energy has been devoted to researching and developing hand-held OAI platforms across the spectrum of OAI methods [14,16,21,33,34,36–38,46,62,67–69,72–99]. These efforts are summarized in Table 1. However, despite the recent explosion of literature reporting hand-held OAI platforms and their uses (Fig. 3), no comprehensive review of such hand-held platforms has yet been published. Therefore, this article attempts to fill this gap to provide readers with a sense of the current state-of-the-art of hand-held OAI platforms from a methods-based viewpoint and provide insight into the direction in which the hand-held OAI field is headed; however, we note that this is not meant to be a review of all OAI technology with clinical potential, nor is it meant to be a comprehensive review of benchtop platforms.

2. Instrumentation for hand-held methods of optoacoustic imaging

In OAI, cross-sectional or volumetric images of tissue are built by analyzing recorded optoacoustic signals that are generated within the tissue. Techniques vary between OAI methods.

OACT image formation remains relatively complicated, becoming in many ways a field of its own, with a multitude of image reconstruction methods and algorithms that have been reported in the literature [8]. Each of these has their own advantages and limitations, and it is up to the discretion of the research team to decide which to use on the basis of their specific device and application. Typically, cross-sectional OACT images are made by using a two-dimensional array of ultrasound sensors [6]. Volumetric images, on the other hand, are typically produced using a three-dimensional array of sensors or by scanning a two-dimensional array of sensors [1,45]. Interested readers who would like to know more about image formation in OACT are referred to reference [103] for more details.

In OMe, an “out of focus” scanning method is typically used [23]. This involves using a focused transducer; the focal point is placed just above the tissue surface and treated it as a virtual detector. This is in contrast to other methods, where the focal point, if there is one, of the sensor or sensor array is inside the tissue. The single transducer is raster-scanned across the sample, and then tomographic image forming methods, similar to OACT, are used to create a cross-sectional or volumetric image [17,18]. This method of OMe is termed raster-scanning optoacoustic mesoscopy (RSOM).

With OMi, imaging is more straightforward: a single sensor and/or excitation source is rastered across a sample. At each point, a one-
A one-dimensional image is created in the axial direction, as either one or both of the excitation light and/or the acoustic sensitivity field (when the sensors is most sensitive) are focused along this direction [1,7]. These one-dimensional images are then stitched together to form a two-dimensional or three-dimensional image. In any imaging method, however, the quality of the image formed – as well as the overall performance of the platform – depends on both the equipment used for optoacoustic signal excitation and the equipment used to detect the resulting optoacoustic signals.

2.1. Light sources

Light sources in OAI are often chosen based on their pulse length, pulse repetition rate, and the wavelength, or range of wavelengths, they produce. It is crucial to incorporate components with sufficiently short pulse lengths because pulse length is related to resolution; as the pulse...
length increases, the maximum imaging resolution a platform can achieve decreases [70]. For OACT, typical pulse lengths range from 10–20 nanoseconds. For high-resolution methods (OR-OMi, AR-OMi, and OMe), pulse lengths are typically a few nanoseconds or less.

Pulse repetition rate describes how quickly a light source can fire successive pulses of light. High pulse repetition rates are not typically necessary for OACT because just one pulse is needed per image due to the use of sensor arrays which gather multiple signals simultaneously. Typical repetition rates in OACT range from 1025 Hz. In OMe, AR-OMi, and OR-OMi, where raster scanning is used, high repetition rates are needed for quick imaging. This is because a laser pulse is needed at each raster scan point, so repetition rates in the kilohertz range are desirable for fast imaging.

The wavelengths that the light source can produce is crucial for any OAI platform. The light wavelength, or range of wavelengths, ideally is only absorbed by the target compound. For multispectral OAI, how quickly the light source can alternate between wavelengths is also taken into account. This is because fast wavelength tuning is necessary to allow for quick, accurate spectroscopic imaging [89]. A common complication that often arises in multispectral OAI is the motion artifacts that result from, for example, the patient’s pulse. This necessitates that multispectral imaging be performed in short enough time spans that these motion effects become negligible [89]. This necessitates quick wavelength tuning and pulse repetition rates.

Lasers are traditionally used as light sources for OAI due to their spectral purity and short pulse lengths. As light-emitting diode (LED) technology has become more advanced, LEDs have become common in OAI [1,72]. The principle drawback of using LEDs is that their pulse lengths are much longer than traditional laser sources, which degrades the quality of the resulting image [104]. This occurs because image resolution is related to the pulse length of the light source used; as the pulse length increases, the maximum imaging resolution a platform can achieve decreases [70].

Alternatively, pulsed laser diodes (PLDs) have been used in OAI platforms; however, their low energy output has limited their functionality [1,86]. The effect of optical energy is intuitive: increasing the energy increases the strength of the optoacoustic response, so high energies are desirable when choosing a light source for an OAI platform.

2.2. Sensors

There are two main classes of ultrasound sensors commonly used in OAI: the traditional ultrasound transducer, which uses piezoelectric elements [105], and Fabry-Perot Interferometers (FPIs) [6,71,106]. The primary limitation of piezoelectric transducers is that they are opaque, which creates complications in delivering light to the tissue. The principle advantage of FPIs over piezoelectric transducers is that the sensitivity of FPIs does not decrease with decreasing element size, as is the case with piezoelectric elements. This allows FPIs to be approximated as point receivers, which in turn allows for more accurate imaging [6,105]. FPIs can also be made to be transparent, simplifying the delivery of light to the tissue [6,105]. The main drawback of FPIs, however, is that the sample must be raster-scanned, which slows data acquisition in comparison to piezoelectric transducers [107]. Due to these drawbacks, while FPI sensors have great utility and potential in OAI, they have not yet been incorporated into any hand-held devices described in the literature.

Beyond these two classes, some non-contact methods of detecting optoacoustic waves have also emerged. For example, one such method measures the displacement of the sample tissue surface due to optoacoustic waves using low-coherence interferometry; it is limited, however, by the necessity of coating the sample in a layer of mineral oil [108]. Another non-contact method of detecting optoacoustic waves is performed by measuring the change in the refractive index of the sample surface caused by optoacoustic waves [48], while yet another method uses holography [109]. However, while non-contact methods have intriguing potential, their primary limitation is that they have not yet demonstrated the ability to image anything deeper than several millimeters in tissue [48,108,109]. In the following sections, we will explore common combinations of light sources and sensors for each OAI method that has been adapted for hand-held imaging, beginning with OACT.

As mentioned previously, the resolution of an OAI platform can be limited by the properties of the excitation light used, but resolution can also be limited by the characteristics of the ultrasound detection equipment employed. So far, all reported hand-held OAI platforms use piezoelectric transducers, and the maximum theoretical resolution that can be achieved by a transducer or transducer array is dependent on the geometry of the array and its central frequency. When selecting or designing a transducer, or transducer array, for a particular application, these constraints need to be taken into consideration.

For OACT, arrays of piezoelectric ultrasound transducer elements are used, of which there are three geometries: linear, cylindrical, and spherical. Linear and cylindrical piezoelectric ultrasound transducer arrays are typically used for two-dimensional imaging, and spherical piezoelectric ultrasound transducer arrays are used for three-dimensional imaging [73,77,78]. The axial resolution of each array type is a function of the frequency response of the array. This can be described using Eq. (1), where \( \lambda_c \) is the wavelength of high cut-off frequency of the array [70]. The lateral resolution of a linear array can be described using Eq. (2), where \( w \) is the width of each sensor element. The lateral resolution of cylindrical and spherical arrays can be described using Eq. (3), where \( d \) is the distance from the center of the scanned area to the resolved point, \( r \) is the radius of the array.

\[
R_{A, OACT} = 0.6\lambda_c \tag{1}
\]

\[
R_{L, OACT} = \sqrt{R_{A, OACT}^2 + w^2} \tag{2}
\]

\[
R_{L, OACT} = \sqrt{R_{A, OACT}^2 + ((d/r)w)^2} \tag{3}
\]

In AROMi, a single ultrasound transducer is used to detect optoacoustic signals [6]. The lateral resolution of AR-OMi is a function the numerical aperture of the lens used to focus the acoustic beam (NA), the photoacoustic center frequency \( f_c \), and the speed of sound in the tissue \( c \) [20]. This can be described using Eq. (4). The axial resolution of AR-
OMi can be described using Eq. (5).

\[ R_{OAR-OMi} = \frac{0.71c}{NAf} \]  
\[ R_{A,OMi} = \frac{0.88c}{f} \]  

Like AR-OMi, the OR-OMi method also uses one ultrasound transducer to detect optoacoustic signals. The transducer may either be focused or unfocused. The lateral resolution of OR-OMi is a function of the numerical aperture of the lens used to focus the light (A) as well as the wavelength of light used (λ) [20]. The relationship can be expressed mathematically using Eq. (6). The axial resolution can also be described using Eq. (5), as it depends on the ultrasound transducer.

\[ R_{LO,OMi} = \frac{0.51f}{NA} \]  

Another key limitation that is imposed upon OAI is the nature of acoustic wave attenuation in tissue. Higher frequency ultrasound waves are attenuated more than lower frequency ultrasound waves over the same distance. This causes limitations on achieving both high resolution and deep imaging depths, with tradeoffs between both. As a result of this, OACT platforms, which have relatively low resolutions, typically use transducers with central frequencies between 5–20 MHz, and can achieve relatively deep imaging depths. Higher resolution platforms (OMe, AR-OMi, and OR-OMi) typically use transducers with central frequencies between 1050 MHz, with some extending up to 180 MHz, but have shallower imaging depths [18].

In the following sections, we will explore common combinations of light sources and sensors for each OAI method that has been adapted for hand-held imaging, beginning with OACT.

2.3. Optoacoustic computed tomography

In conventional hand-held OACT, two-dimensional and three-dimensional images are made using unfocused light and an array of US transducers [1,20]. To the authors’ knowledge, there are two companies producing hand-held OACT platforms that have appeared in published research: iThera Medical and VisualSonics [37,73,78,82,85]. The hand-held OACT platforms produced by these companies are summarized in Table 2. The first hand-held OACT platform that utilized a linear array was developed by Niederhauser et al. (2005) and has been used to image blood vessels in human skin [92,97]. Since then, the technique has been used by VisualSonics to develop a fully-featured, commercialized, line of hand-held OACT platforms for research use. These have been used in a multitude of studies, although none are approved by the FDA for clinical diagnostics [73,79,82,85,92]. Other research teams have developed their own systems independently [74,99] or in collaboration with industry partners [87,88].

2.3.1. Linear piezoelectric ultrasound transducer arrays

Linear, piezoelectric, ultrasound transducer arrays were first introduced because conventional US imaging platforms could be easily modified for OACT imaging, simplifying the development process for OACT platforms [92]. This also allowed for easy implementation of dual modality US-OACT imaging platforms. In these platforms, the linear arrays were commonly focused in the elevation direction, known as cylindrical focusing, onto the imaging plane to reduce the strength of signals arising from outside the imaging plane. However, the piezoelectric ultrasound transducers and transducer arrays were opaque, so light could not be delivered to the tissue directly under the transducer when it was in direct contact with the tissue. In order to work around this complication, several compensating light delivery approaches have been developed.

The first approach to overcome the opacity of the piezoelectric ultrasound transducers/transducer arrays is to simply deliver light to the sides of the transducer/transducer array and to rely on the scattering of light in the tissue to deliver light to tissue that is directly underneath the transducer/transducer array [73,85,87,92]. A schematic of this approach can be seen in Fig. 4. For the purpose of this review, we shall explore the studies mentioned previously in this subsection as an illustrative sample of the work done using this method to overcome the opacity of the transducers/transducer arrays.

Needles et al. (2013) reported the use of a linear array with 256 elements and a central frequency of 21 MHz in a dual-modality ultrasound-OACT (aka US-OACT) imaging platform [92]. The transducer used was acquired from VisualSonics. Light was provided by a tunable Nd:YAG laser operating between 750 and 850 nm with a 20 Hz

Table 2

| Company         | System          | Method          | Resolution A | Depth   | Max Speed | SNR | Sensitivity          |
|-----------------|-----------------|-----------------|--------------|---------|-----------|-----|----------------------|
| Visualsonics    | Vevo LAZR-X     | 2D/3D US-OACT/ US-MSOT | A: 110 μm, L: 220 μm | 10-20 mm | 0.05 s | 30 dB +/- 10 dB | < 100 nM dynes, nanostructures |
| iThera Medical  | Acuity/ Explorer C50 | 2D/3D US-OACT/ US-MSOT | A: 10 μm, L: 40 μm | 3.5 mm | DNR | DNR | DNR |

Adapted from [82].
repetition rate. This platform was used to generate 2D and 3D images that were used to visualize the oxygenation of blood within the jugular vein in mice, as well as within murine tumors. The authors noted that this device may be useful in pre-clinical monitoring of changes in tumor oxygenation during therapy or studying tumor hypoxia.

García-Uribe et al. (2015) used an ultrasound imaging platform modified for USOACT for imaging SLNs tagged with methylene blue dye [87]. A Q-switched Nd:YAG laser was used to pump a tunable dye laser operating at 10 Hz and 667 nm, chosen for its selective absorption by the dye relative to surrounding compounds. The team used the platform to assist surgical placement of a titanium marker clip on a SLN. The authors noted that this work paves the way for the use of this platform in guiding SLN biopsies (Fig. 5).

Zhou et al. (2015) used an OACT platform from Visuonics Inc. to generate 2D and 3D images of melanoma tumors in mice [85]. The transducer had a central frequency of 21 MHz and was made up of 256 elements. The array was focused cylindrically with a focal length of 15 mm. Laser light was supplied by a tunable optical parametric oscillator (OPO), which provided light at 20 Hz pulse repetition rate, at a wavelength of 689 nm, which is strongly absorbed by melanin. An imaging speed of 5 Hz was achieved. Scanning of the 2D array allowed for volumetric imaging of the tumor. The authors noted that this platform could be applied in the clinic to assist in diagnosing melanomas because volume, which the platform can measure, is a better metric for tumor diagnosis than the current metric of tumor thickness. This imaging platform was also applied to imaging melanoma tumors in patients in a clinical trial [73]. The authors noted that the platform was able to image tumors at depths up to 10 mm and that the resulting depth measurements were in good agreement with depths measured via biopsy. The authors noted that this device could be applied to assist in surgical intervention. The principle drawback of this approach, however, was that many acoustic signals will originate outside of the transducer, outside of the acoustic sensitivity field, which can result in a decrease in the quality of the resulting image [88].

The second approach used to overcome the opacity of piezoelectric ultrasound transducers/transducer arrays is to place an optically transparent spacer to offset the transducer from the tissue. Laser light, delivered by an optical fiber, can then be directed to tissue underneath the transducer. Adapted from [74].

Zhao et al. (2017) demonstrated a USOACT probe for imaging the human breast [74]. To do this, the team modified a commercially available, ultrasound imaging platform that used a piezoelectric ultrasound transducer array with 192 elements and that had a central frequency of 5.8 MHz. A Q-switched Nd:YAG laser was used to provide light, which operated at 1064 nm and a pulse repetition rate of 10 Hz, with a thickness of 4 mm was placed between the probe and the tissue. The team demonstrated their system by imaging the breast of a 47-year-old patient as a case study. The platform was shown to be able to image the vasculature in the breast and was able to demonstrate the importance of proper optical fluence compensation in optoacoustic image formation. The main drawback of using a spacer is that in moving the sensor array away from the target tissue, the SNR is reduced due to the increased distance the acoustic waves must travel to reach the sensor. [6,105].

The third approach for overcoming the opacity of piezoelectric ultrasound transducers/transducer arrays is to manufacture transducer arrays so that optical fibers can be placed between the individual elements. This approach is utilized in the report by Ida et al. (2015) to image burn wounds in rats [81]. A schematic of this can be seen in Fig. 6. The intent of this approach is to cause the platform to function much like platforms where the transducer array is illuminated from the side. In this report, the transducer array consists of eight elements and has a central frequency of 10 MHz. The light source is a fiber laser that outputs light with a wavelength of 532 nm at a repetition rate of 500 Hz. The platform is able to image burns at a rate of 5 Hz, and the burn depths determined by the platform are reported to be in good agreement with those determined by histology. While the idea is novel, it still suffers from light illuminating tissue from the sides of the elements, which causes many signals to originate outside of where the ultrasound array is most sensitive, which in turn decreases the resulting quality of the image.

While OACT platforms that use linear arrays have some advantages, such as relatively small array size and ease of implementation, over
other transducer array geometries, their major drawback is their resulting image quality [69]. The viewing angle of linear arrays is inherently limited, reducing the overall resolution of the system as well as being reduced their ability to image sloped surfaces.

2.3.2. Curved (cylindrical) piezoelectric ultrasound transducer arrays

Fortunately, curved arrays provide excellent resolution by increasing the viewing angle of the array in comparison to linear transducer arrays [94]. Additionally, curved arrays can also reduce image artifacts and have greater ability in imaging sloped surfaces [36,69,94]. Moreover, while the sensitivity of a linear array is greatest closest to the array surface, curved arrays have greatest sensitivity at the center of the circle they encompass [69,110]. This space between the surface of the array and where it is most sensitive, called the field of view (FOV), allows for light to be delivered directly to tissue within the FOV. Most curved arrays used in hand-held OACT platforms provide 180-degree coverage or less [33,34,36–38,67,77]. As a rule of thumb, this limits the FOV to a volume with a radius that is about one quarter of the radius of the curved array, so these advantages come at the expense of array size [69,110]. This is in contrast with linear arrays, where the FOV runs the entire length of the array (Fig. 7).

The first hand-held OACT (MSOT) platform that used a curved array was reported by Buehler et al. 2013 and was demonstrated using a platform that was developed in-house [67]. The system used a tunable OPO with an output range of 680–980 nm pumped by an Nd:YAG laser with a repetition rate of 50 Hz. The piezoelectric ultrasound transducer array consisted of a curved array of 128 elements with a central frequency of ~8 MHz. The team demonstrated the imaging capabilities of the platform by imaging the wrist of a volunteer, using blood as the primary endogenous contrast agent. The team also observed changes in blood oxygenation and total blood volume in a volunteer’s finger when blood flow to the finger was obstructed. The team noted they hoped to apply this technology to clinical applications related to cardiovascular disease.

Since then, multiple studies have been conducted using similar configurations [36,38,77]; these platform configurations have been frequently used in OACT (MSOT) studies [32–34,37,67,102]. Much of this work has been done as a collaboration between iThera Medical and the Helmholtz Zentrum München. A basic schematic of the operation of a curved array can be seen in Fig. 8. In order to facilitate acoustic coupling between the tissue and the transducer array, the cavity is often filled with water and sealed with a transparent membrane. In order to explore the capabilities of OACT (MSOT) platforms using curved array transducers, we will review several selected studies that have been recently published below.

Dima and Ntziachristos (2016) demonstrated the use of an OACT (MSOT) platform that utilized a curved array to image the thyroids in two female volunteers [38]. The curved array was made of 64 elements encompassing a circle with a radius of 40 mm and an angular coverage of 172°. The array had a central frequency of 7.5 MHz. 800 nm light was delivered by a pulsed laser system that operated at a repetition rate of 10 Hz. The team was able to visualize the outline of the thyroid as well as vasculature structures 20 mm deep within the tissue. The authors noted that the device could possibly be applied to assist in the diagnosis of thyroid disease as well as guiding fine needle aspiration.

Taruttis et al. (2016) used a platform with a curved array for OACT (MSOT) imaging of vasculature in the feet of healthy volunteers [36]. The curved array consisted of 128 elements with a central frequency of 8 MHz and a focal length of 20 mm. The angular coverage of the array was 135°. Light was supplied by a diode-pumped Nd:YAG laser pumping an OPO that output light at wavelengths of 790 nm, 750 nm, 800 nm, and 830 nm. Additionally, the platform was capable of performing multispectral imaging at an imaging speed of 2.5 Hz. The team was able to demonstrate the platforms’ ability to image both large and small vessels. The authors noted that potential clinical applications of the platform include assessing diseases as well as visualizing the results of stent placement.

Diot et al. (2017) used an OACT (MSOT) platform with a curved array to identify OA-resolvable features of breast cancer [33]. The curved array consisted of 265 elements with a central frequency of 5 MHz. The radius of the curved array was 60 mm and had an angular coverage of 174°. A tunable pulsed laser was used for illumination, operating at repetition rate of 50 Hz and 28 wavelengths between 700 and 970 nm. The team reported achieving an imaging speed of 2 Hz. The platform was able to resolve four separate target compounds: oxygenated hemoglobin, deoxygenated hemoglobin, lipids, and water. The team found that they were able to visualize vascular patterns and the disruption of tissue layers associated with tumors with this platform. The researchers further explained that this platform could be used to assess tumor function and the effects of neoadjuvant chemotherapy.

Knieling et al. (2017) used a commercially available OACT (MSOT) platform with a curved array to assess Crohn’s disease activity in the bowels in a clinical trial [32]. The platform used near infrared (NIR) light to target hemoglobin as an endogenous contrast agent because tissue perfusion is associated with Crohn’s disease activity. Six wavelengths were used in imaging, ranging from 700 to 900 nm, and were used to spectrally determine total hemoglobin, oxygenated hemoglobin, and deoxygenated hemoglobin within the target tissue. The clinical study recruited 91 patients. Endoscopic scoring, histologic scoring, and ultrasonography were all used as reference tests. Using data obtained from the platform, the team was able to distinguish between active and non-active forms of Crohn’s disease with a p-value less than 0.001. The team noted that the results of the study were encouraging.
and indicated that MSOT could be used to distinguish active forms of Crohn’s disease from non-active forms.

2.3.3. Spherical piezoelectric ultrasound transducer arrays

When compared to curved arrays, the advantage of using a spherical array is its ability to perform rapid volumetric imaging, which is crucial for studying certain dynamic physiological phenomena, such as visualizing blood oxygenation for diagnostic purposes [16,46,68]. Unfortunately, this comes with certain disadvantages. A comprehensive comparative study of the performance of spherical and curved arrays demonstrated that a major weakness of current spherical arrays is their reliance on light scattering to deliver light to the entire imaging volume [37]. In highly absorbing tissues, this limits the ability of the spherical array to image the entire volume accurately. The authors of that study explained that, until a solution is developed, OACT platforms that utilize spherical arrays may best suit imaging superficial tissues, while OACT platforms that utilized curved arrays are better for targets located deeper in the tissue.

Spherical arrays were first implemented in a hand-held OACT platform by Deán-Ben, Özbek, and Razansky (2013), using a custom-made spherical array that was then modified by the team to improve its performance [94]. The configuration consisted of a hemispherical transducer array that had an optical fiber placed in the middle of the array (Fig. 9). Light scattering was used to deliver light throughout the imaging volume [37]. The cavity between the array and the tissue was filled with water and sealed with a transparent film to facilitate acoustic coupling. The spherical array consisted of 256 elements, an angular coverage of 90°, and a central frequency of 4 MHz. An OPO with a repetition rate of 10 Hz and wavelength of 800 nm was chosen because it is the isosbestic point of the hemoglobin, which was used as the endogenous contrast agent in the study. The platform was able to image vasculature in the arm and forearm of a healthy volunteer at a rate of 10 Hz. The authors noted that this device could be used in dynamic tracking of hemodynamic events and circulating cells. This innovation spurred multiple other studies [37,68,78,83,93] and has been integrated with a number of OACT platforms to good effect [16,89,102]. Some of the most recent and compelling work was conducted as a collaboration between iThera Medical and the Helmholtz Zentrum München [16,78], which will be reviewed here.

Fort et al. (2016), used an OACT (MSOT) platform with a spherical array to assess morphometric parameters of hair follicles, surrounding lipids, and associated capillary beds [16]. The transducer array consisted of 512 elements that had a central frequency of 10 MHz and a solid angle coverage of 140°. Light was supplied by the pulsed laser system, which was capable of operating at a repetition frequency of 100 Hz and was tunable between wavelengths ranging from 660 to 1300 nm. Heavy water was used to fill the cavity between the sensor and the tissue because it absorbs less light than water in the wavelength range used. The system was able to image an entire hair follicle, resolving four separate compounds: melanin, lipids, oxygenated hemoglobin, and deoxygenated hemoglobin. The authors state that while the results of the study are encouraging, they were not confirmed using a different method of measurement. The authors noted that histopathology could be a valuable method of analysis, but other methods would be needed to validate longitudinal studies. The authors hoped to apply this technology to further study hair follicles and to visualize the effects of various treatments of disorders such as hair loss.

Attia et al. (2017), utilized an OACT (MSOT) platform with a spherical array to characterize non-melanoma skin cancers [78]. The team recruited 21 patients and used the platform to determine tumor dimensions in the patients. Illumination was provided by a tunable OPO laser that operated at a repetition rate of 10 Hz and wavelengths ranging from 700 to 900 nm. The platform was able to provide multispectral images, differentiating between the optoacoustic targets (melanin, oxygenated hemoglobin, and deoxygenated hemoglobin) in real time. The authors concluded that while the study included only a limited number of patients, they were confident the platform could be applied to mapping skin cancers and could be used to guide surgical interventions.

2.4. Optoacoustic mesoscopy

In OMe, a single transducer is used for signal acquisition, along with broad illumination of the tissue surface [23,26,40]. The instrumentation in OMe is unique in that the focal point of the array is placed just above the tissue surface, treating the focal point as a point detector. By offsetting the transducer from the surface, there is enough space to directly illuminate the target tissue. Hand-held OMe has taken the form of RSOM and was first demonstrated by Aguirre et al. (2017); RSOM technology is relatively new, and no commercial systems exist at this time [18].

In Aguirre et al.’s study, the team developed a scanning head attached to an articulated arm that allowed for easy placement of the platform on the target tissue (Fig. 10). The scanning head consisted of a spherically-focused, piezoelectric ultrasound transducer with an ultrabroadband (UB) detection range that extended from 10 to 180 MHz. The transducer had a diameter and focal distance of 3 mm. To enable raster scanning, the spherical array was fixed to motorized stages. The bottom of the scanning head was sealed with an optically and acoustically transparent plastic, and the space between the transducer and the plastic was filled with water to provide acoustic coupling. The team employed a laser system with a pulse length of less than 2 ns, allowing the generation of ultrasound waves across a broad frequency spectrum. Illumination of the tissue was accomplished using two rectangular
bundles of optical fibers placed on opposite sides of the spherical array. The received signals were separated into two groups based on frequency. These two groups of data were reconstructed and normalized separately to account for the attenuation of relatively low intensity of high-frequency sources. The two images were then co-registered to allow the visualization of high intensity, low frequency, low resolution targets alongside low intensity, high frequency, high resolution targets. Using this method, the team was able to image a 4 mm × 2 mm area in 70 s with a lateral resolution of 18.4 μm, an axial resolution of 4.5 μm, and an imaging depth of 1.5 mm. The team used the device to visualize changes in skin features in patients with psoriasis.

A similar platform was also demonstrated in a study by J. Aguirre et al. in 2018 [17]. The difference between this platform and the one previously described was that the 2018 platform used an ultrasound transducer with a central frequency of 55 MHz and an ultra-broadband (UB) detection range that extended from 10 MHz to 120 MHz. This transducer was chosen because the lower central frequency allowed signals from deeper in the tissue, where the region of interest was located, to be received. This transducer provided a lateral resolution of 30 μm and an axial resolution of 8 μm. The team demonstrated the utility of the device by visualizing vascular biomarkers in nailfold capillaries in patients with systemic sclerosis.

2.5. Optoacoustic microscopy

As mentioned previously, Optoacoustic Microscopy (OMi) is used to image small sections of tissue, such as capillary beds. This OAI method can be divided further into two classes based on how resolution is achieved: acoustic resolution (AR-OMi) and optical resolution (OR-OMi). In AR-OMi, the resolution of the system is determined by the acoustic detection components, whereas in OR-OMi, the resolution is determined by the properties of the excitation light. In order to capture the continuous scalability of OAI, so-called ‘switchable’ or ‘hybrid’ AR- and OROMi systems have been developed [21,22]. These systems can employ either AR- or OR-OMi resolution methods by simply adjusting some of their components, demonstrating the power of OAI scalability.

2.5.1. Acoustic resolution optoacoustic microscopy

Dark-field illumination is one of the most common configurations for AR-OMi, and has recently been integrated into a hand-held probe (Fig. 11) [6,14,111]. In dark-field illumination, a piezoelectric ultrasound transducer is offset from the tissue, and acoustic coupling is accomplished using water. Laser light is fired around the transducer, obliquely illuminating the tissue under the transducer. If the transducer is small enough, laser light can be delivered normal to the tissue, and light scattering is used to deliver light to tissue that is underneath the transducer (Fig. 12) [14]. Images are made by either scanning the transducer in a straight line, to produce a cross-sectional image, or raster scanned, to produce a volumetric image.

Fig. 11. Partial, cut-away view of dark-field illumination of tissue in AR OMi. Laser light is directed around the transducer, which is offset from the tissue. Adapted from [111].

Fig. 12. Partial, cut-away view of direct illumination of tissue in AR OMi. Laser light is delivered to the tissue next to the transducer and a normal incidence angle using optical fibers. Illumination of acoustic targets beneath the transducer is facilitated by the scattering of light. Adapted from [14].

To the authors’ knowledge, no hand-held platform has been developed that harnesses the resolving power of AROMi, which has been demonstrated to be able to achieve 15 μm axial resolution and 45 μm lateral resolution in benchtop setups [19,63]. One hand-held platform has been developed, by Zhou et al. (2014); this platform had a lateral resolution of 230 μm and an axial resolution of 59 μm [14]. Due to this relatively low resolution, it may be more appropriate to designate this as a mesoscopic imaging platform, despite its configuration as an AROMi platform [12]. Zhou’s design, a small, 25 MHz piezoelectric ultrasound transducer was used to image melanoma tumors in mice. The light was delivered to the hand-piece using an optical fiber that illuminated the area around the transducer at a normal incidence angle. Monte-Carlo simulations were performed to demonstrate the diffusion of light from the side of the transducer to the target underneath it. This configuration was chosen because previous iterations of the design, which delivered light directly to the melanoma, were unable to illuminate the entire tumor volume due to strong optical attenuation within the melanoma itself. This limited the platform’s ability to image deep melanomas because light could not be delivered to the base of the melanoma. By delivering light to the side of the region of interest, the base of the melanoma could be illuminated by the light scattered around it. The transducer and optical fiber were connected to a motorized translational stage and used to produce cross-sectional images. Excitation light with a wavelength of 650 nm was chosen because it is strongly absorbed by melanoma, but not hemoglobin or water. The authors noted that the practical limitation of the platform was the scanning speed, which was limited by the laser’s repetition rate.

Fig. 13. Depiction of an optoacoustic beam combiner (OABC) used in OR OMi. This OABC contains an optically reflective layer that does not affect acoustic wave propagation. Incident laser light is placed orthogonally to the acoustic sensitivity field of the transducer, and the two are combined in the OABC. The laser is raster scanned by a mirror. Adapted from [80].
2.5.2. Optical resolution optoacoustic microscopy

The most common configuration for an OR-OMi platform uses a so-called ‘opto-acoustic beam combiner’ (OABC), also called an ‘opto-ultrasound combiner’, to coaxially align the laser with the detection column of the transducer [21,98]. One manifestation of this configuration can be seen in Fig. 13 [80]. The principle of an OABC is to use an object that has either an optical or acoustic reflective layer to align the incident laser light with the acoustic sensitivity field. The incident laser beam is orientated orthogonally to the acoustic sensitivity field, and the two are combined at the reflecting layer. Volumetric imaging has been achieved by rastering the laser point and, if the transducer is focused, the acoustic sensitivity field across the tissue surface.

To the authors’ knowledge, three hand-held OROMi platforms have been developed, but none are currently commercially available [80,95,98]. The first platform to be reported, by Hajireza, Shi, and Zemp (2011), consisted of a 10 MHz focused transducer coupled to an OABC that contained an acoustically reflective surface [95]. Laser light was delivered using an image guide fiber, and scanning of laser light occurred as light was being coupled into the fiber. Fast imaging of microvasculature in the ear of a mouse was accomplished by utilizing a scanning mirror to raster scan the acoustic sensitivity field and excitation light over the region of interest. The excitation light source, a pulsed fiber laser producing 532 nm light with a repetition rate of 160 kHz, was likely chosen to target hemoglobin and to facilitate quick imaging.

The system was able to achieve images with a lateral resolution of 7 μm scanned over a 0.4 mm × 0.4 mm surface at a rate of 2 Hz and was limited by the scanning speed of the mirror. The authors noted the platforms’ potential uses in clinical and pre-clinical applications including assessing melanoma sectioning and imaging angiogenesis, among others.

The second platform was reported by Lin et al. (2016) (similar to Fig. 13) [80]. A 50 MHz transducer was used to detect the optoacoustic signal, and a mirror was used to scan the laser light across the sample. A fiber laser with a pulse repetition rate of 88 kHz that output light with a wavelength of 532 nm was used as the light source. Similar to the previous study, this light source was likely chosen to provide fast imaging as well as provide a wavelength that is primary absorbed by hemoglobin. The fast scanning mirror allowed a relatively large area, 2.5 mm × 2 mm, to be scanned and allowed an imaging speed of 2 Hz. The researchers reported achieving a lateral resolution of 5 μm and a maximum imaging depth of 540 μm. The research team demonstrated the abilities of this platform by imaging the blood vessels under a cuticle in human skin, and a red mole on a healthy volunteer’s leg. The authors noted that this device could be used for intraoperative assessment of cancer margins.

The third platform, reported by Park et al. (2017), consisted of a similar setup, using a scanner to raster the excitation light and acoustic sensitivity field across the sample [98]. They were able to produce a small probe, which was circular in shape and had a diameter of 17 mm and length of 31 mm. The team constructed a waterproof, compact scanning mirror, which allowed for its integration into a small probe. The ultrasound transducer used had a central frequency of 50 MHz, and the platform had an axial resolution of 12 μm and lateral resolution of 30 μm. The probe has a maximum field of view of 2.8 mm × 2 mm. Light was supplied using a Q-switched diode-pumped solid-state laser operating at 532 nm and a repetition rate of 50 kHz. The authors noted that the slow imaging speed, 20 s per volumetric frame, could be improved by using a laser with a faster repetition rate and by redesigning the mirror to allow faster scanning. To demonstrate the utility of their platform in human imaging, the team imaged a mole on a volunteer’s finger. The authors explain that this imaging platform could be best applied to imaging and diagnosing melanomas.

3. Discussion

Recently published papers on hand-held OAI platforms show that OACT has, by far, become the most advanced technology in the OAI modality suite. Multiple off-the-shelf systems are available from iThera Medical and VisualSonics, with many being used in research and clinical studies. The utility of OACT platforms has been further broadened by the development of dual-modality USOACT imaging systems [75]. There are, however, ways that current platforms could be improved. As previously described, the main limitation with OACT platforms is that piezoelectric transducers used are opaque, blocking any path of laser light to tissue directly underneath the transducer while the transducer is in direct contact with the tissue. While some modifications have been developed to overcome this problem, they do not allow for the full imaging capabilities of the linear transducer arrays to be realized. Some preliminary work has been conducted that uses waveguides to deliver light to samples directly underneath the transducer, minimizing the size of the spacer [112]. This minimizes the reduction of the transducers’ FOV when a spacer is included, therefore improving the resulting image quality. Alternatively, bench-top OACT platforms utilizing FPI have been developed, demonstrating transparent acoustic detectors, but these have yet to be translated into a hand-held platform [107,113].

Existing OAI platforms are also limited by the need for many transducer elements to create real-time, two-dimensional and three-dimensional images, complicating instrumentation [1]. In order to simplify platforms, acoustic delay lines are being investigated to allow one transducer to detect ultrasound signals from several positions in the tissue [84,90]. This allows for OACT to be accomplished using much simpler setups.

With regards to OMI platforms, OR-OMi has received more attention than AR-OMi based on literature counts of published studies. Authors of recently published papers in OROMi note that the chief limitation in the method is the speed of the scanning mirror [80]. As further improvements are made to OR-OMi platforms, clinical application is just around the corner.

Lastly, OMe (RSOM) is a relatively recent addition to the OAI modality suite, but presents a powerful method of imaging structures on the micron scale, rivaling the resolving power of hand-held OR-OMi while producing images from greater depths within tissue. So far, only two hand-held platforms have been developed, but as other applications are explored, more are sure to come.

A major current limitation in OAI is compensating for variable light fluence throughout the region of interest. Optoacoustic signal strength is proportional to the optical absorption of the tissue and the local fluence. In tissue, fluence can vary greatly, making signals originating from deep in the tissue appear weak [74]. This can obscure deep structures. Zhao et al. (2017) used a finite element method to model fluence within breast tissue, and used this to compensate for fluence in optoacoustic images of breast vasculature. The weakness of this solution is that if the optical properties of the tissue deviate from the assumed properties in the model, the measured values could be inaccurate. This problem becomes even more complicated in spectroscopic imaging. This is due to the dependence of fluence on both depth and the wavelength of light used. Incorrectly compensated signals can greatly affect the accuracy of spectrally resolved components [35]. Recently, Tzoumas et al. (2015) demonstrated the use of ‘eigen-spectra MSOT’, a previously unexplored method, which is based upon the idea that a few base spectra can be used to predict fluence in tissues with arbitrarily varying optical properties [35]. They demonstrated that this technique can be used to reduce the error in measuring oxygen saturation in deep tissues by 3–8 fold in comparison with more common linear fitting models.

Another limitation for OAI platforms is device cost. Many OAI devices use OPOs, dye-based lasers, or Nd:YAG lasers, all of which are expensive [8]. Commercial systems can cost close to one million dollars [114].

Despite these current limitations, OAI is continuously being applied in new areas. For example, Zhou, Liang, and Wang (2016) demonstrated the use of a hand-held OACT platform in vivo blood flowmetry in humans [79]. The authors note that this information can be used in
the diagnoses and treatment of diseases such as stroke and atherosclerosis. Another exciting front in OAs is the detection of circulating tumor cells (CTCs). Labeled CTCs have been successfully detected in vivo in mice, as well as melanoma CTCs, whose melanin content serves as an endogenous contrast agent [29]. There have also been studies that have detected and captured in vitro CTCs [115]. Here, human blood was mixed with breast cancer cells, tagged using an exogenous agent, and isolated using a benchtop setup.

Intraoperative imaging is another emerging area where OAI is being applied. For instance, it has been noted that OAI could be used to assess blood perfusion in the colon or esophagus during surgery [29,116]. This information could be used to fix anastomotic leakage while surgery is being performed. Additionally, a pilot study demonstrated the use of OAI during surgery on the prostate [101]. The results of the study indicate that a dual modality US-OACT platform could be used during prostate surgery to help surgeons visualize critical tissues. In other applications, US-OACT (US-MSOT) was used to image, in vivo, sentinel lymph nodes marked with a contrast agent [102]. The pilot study, which involved 20 patients, demonstrated for the first time that the method could identify metastasis of melanoma in lymph nodes with 100% sensitivity, which demonstrated the significant impact of a device could have on diagnosis and treatment.

The use of dual-modality hybrid AR-OROMi platforms has also been explored, and was used to visualize changes in tissue caused by low level laser radiation [117]. The authors note that this system could be incorporated into feedback control system of medical procedures, making them safer and more effective. The use of dual modality OAC-TOCT is also being demonstrated [71]. Zabihian et al. (2015) used a portable OACT- OCT system to visualize several skin pathologies. Lastly, many endogenous contrast agents can be used in OAI studies, the use of exogenous contrast agents is an area of important study. Common examples include gold and carbon nanoparticles, small molecule dyes, and organic nanostructures [118]. ‘Smart’ contrast agents, whose optical properties are altered by biological processes in vivo and can be used to monitor such processes, and are an exciting area of growth. Jathoul et al. (2015) demonstrated the use of generating an optoacoustic contrast agent in vivo using the enzyme tyrosinase (Tyr) [106]. In the cell, Tyr forms eumelanin from tyrosine, which is a broadband absorber well suited as a optoacoustic contrast agent. In the study, the team imaged the growth of genetically engineered cells, which expressed Tyr and were injected into nude mice, using a FPI system. This is just one illustrative example [118].

Clearly, the potential impact of hand-held OAI platforms in the clinic is high. OAI can provide a wealth of diagnostic information when treating diseases and conditions such as melanoma tumors [73], breast cancer [33], thyroid cancer [75], and burns [81]. This information could improve the accuracy of diagnoses, aid in early detection of disease, assist surgeons, and improve patient outcomes. In translating OAI methods from benchtop platforms to hand-held platforms, this technology becomes a much more practical clinical tool that will be able to be more widely used for research and patient care [37,71].

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Mason Schellenberg received his B.S. and M.S. in Biological Engineering for the University of Missouri. He has worked in a wide range of research areas, including instrumentation and design of medical imaging devices for clinical applications, benchtop bioreactor design, and investigated novel methods of 3D printing. His current research involves the development of a handheld photoacoustic imaging device.

Heather K. Hunt received her B.S. in Chemical Engineering from Iowa State University, and her M.S. and Ph.D. in Chemical Engineering from the California Institute of Technology. After graduating, she joined the Mork Family Department of Chemical Engineering and Materials Science at the University of Southern California as a Postdoctoral Scholar. She is currently an Associate Professor in the Department of Bioengineering at the University of Missouri, with courtesy appointments in Chemical Engineering and Dermatology. She has been the recipient of an NSF Graduate Research Fellowship, the USC WSE Merit Award for Excellence in Postdoctoral Research, the 3M Non-tenured Faculty Award, and several teaching and mentoring awards. Her research focuses on optoelectronic materials and biophotonics.