Imaging tumor development using next generation raster scan optoacoustic mesoscopy

Cancer is one of the major diseases in the 21st century. Hundreds of billions of dollars have been spent on cancer research in the last half century, but still, our understanding of the disease mechanisms is limited. This is reflected in the small decrease in the death rate caused by cancer from 1950 until today by only 5%. One reason for such a limitation is our limited ability to observe cancer *in vivo*. The main imaging tools such as magnetic resonance imaging, X-ray CT, and fluorescence tomography deliver only bulk information about the tumor. On the other hand microscopic tools, such as multiphoton microscopy and optical coherence tomography scratch only the surface of the tumor, thus it has little access to processes happening deep inside the tumor, or to tumor heterogeneity.

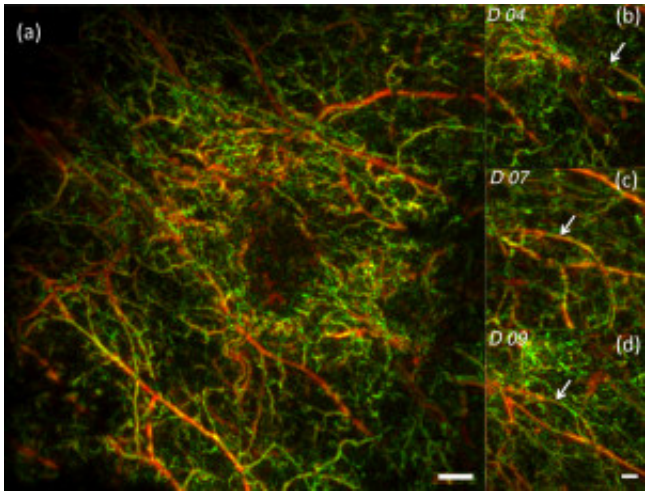

Fig. 1. Full field view of the tumor, imaged at day 4 (a), follow up of a zoomed in region showing the increase in microvasculature (represented by green) as going from day 4 to day 9 (b-d). Scale bars: (a) 1 mm, (b-d) 0.5 mm.

In our recent work „*Pushing the optical imaging limits of cancer with multi-frequency-band raster-scan optoacoustic mesoscopy (RSOM)*“ we introduce a system, which overcomes these limitations. This system is based on the so called “optoacosutic effect” Optoacoustics (also known as photoacoustics) is a physical phenomenon that was discovered in the 1880s by Alexander Graham Bell; this effect tranfers the optical energy through heat into sound. In simple terms, optoacoustics is „listening“ to light. The main contrast generators in optoacoustics are blood and melanin, which allows imaging the morphology of tissue and sensing functional parameters of the same tissue. Optoacoustic imaging works in the mesoscopic regime. Mesoscopy comes from the Greek word „Meso“ meaning in between and „scopy“ from the Greek word „skopein“ meaning „to

look, see“, thus it relates to imaging at scales deeper than what microscopy can reach, and at the same time smaller than where macroscopic techniques, like ultrasound imaging, become efficient.

As previously reported RSOM is capable of imaging with a resolution of 4?40 µm, at depths of several millimeters, and volumes of 1000?10000 times larger than what microscopic techniques can do. Based on these characteristics we investigated the suitability of using RSOM for imaging of tumor neovascularization (or angiogenesis), i.e. the growth of new blood vessels, which is one of the main hallmarks of cancer. The importance of this hallmark is that for a tumor to grow it needs to constant supply of oxygen and nutrients, thus it starts building new blood vessels. On the one hand, monitoring this process is critical for understanding the how tumors work. On the other hand, these newly grown blood vessels are a target of several cancer therapies; being able to monitor them during therapy shows us the efficiency of the therapy, and helps in devising better strategies for therapy.

In our present study we monitored tumor development in a mouse model of melanin cancer over the course of 9 days (see Fig. 1.). With our system we observed an increase in the tumor size, but more importantly, we successfully monitored the growth of new blood vessels, i.e. angiogenesis or neovascularization of the tumor. This kind of imaging technology is unique, and it is very flexible. Our System shows tumor vascularization and neovascularization not only with so far unprecedented high resolution, but on a global scale spanning the complete tumor and the vascular bed surrounding it. We strongly believe this will have a large impact on cancer research and it will help in devising better strategies for cancer therapies in the future.

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