



UvA-DARE (Digital Academic Repository)

Glow with the flow: Quantifying blood flow and photoluminescence signal in biological tissue

Nadort, A.

Publication date

2015

Document Version

Final published version

[Link to publication](#)

Citation for published version (APA):

Nadort, A. (2015). *Glow with the flow: Quantifying blood flow and photoluminescence signal in biological tissue*.

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.



9

OUTLOOK

ABSTRACT This last chapter reflects shortly on the thesis aims and presented results. The chapter continues with an outlook on the combination of the discussed optical techniques in the context of tumour detection, therapy and monitoring of tumour development.

9.1 INTRODUCTION

The role of the microcirculation in the development of a range of diseases dictates the need for good clinical techniques to assess its functionality. Inadequate tissue perfusion by the microcirculation is often an early indicator of more severe pathologies, for example in diabetes and critical diseases [1-3]. On the other hand, an impaired microcirculation functionality can result from an array of cellular processes and its assessment often lacks specificity or sensitivity for pathological processes. Photoluminescence-assisted imaging can enable enhanced molecular contrast in biological tissues, biological liquids or bioassays [4-6]. The quantification of blood flow and photoluminescent signals in the biomedical context can contribute to clinical information relevant to a wide range of potential clinical applications. Since the acquisition of reliable results is of key importance for the advancement of clinical research, considerable effort has been devoted to improving the quantitative evaluation of optical techniques (all first-authored publications in this thesis start with the word 'quantitative!'). This thesis aimed to give a realistic expectation of the abilities of quantitative flowmetry and photoluminescence-based imaging in tissue by experimental and theoretical modelling of light-tissue interactions. Practical guidelines towards quantitative laser speckle flowmetry are presented together with a detailed theoretical background that elucidates the essential aspects for quantification. Experimental optical characterization of the upconversion nanoparticle (UCNP) photoluminescent properties and modelling of this signal in the biomedical context enables assessment of their detectability in clinically relevant scenarios. The quantification of microcirculatory blood flow and the quantification of the upconversion signal in biological tissues both have their individual clinical application niches. In this last section, I will reflect on their powerful combination for the diagnosis and therapy of tumours, and particularly the monitoring and understanding of tumour development.

9.2 QUANTIFYING BLOOD FLOW AND PHOTOLUMINESCENCE SIGNAL IN TUMOUR TISSUE

Angiogenesis is a hallmark of cancer and facilitates accelerated and uncontrollable tumour growth [7, 8]. Enhanced perfusion as well as enhanced permeability and retention of nanoparticles are complementing indicators for the presence of tumours, which can be measured by the two techniques discussed in this thesis. The complex tumour physiology and structural heterogeneity can be assessed by combining information from blood flow mapping and localizing accumulations of UCNPs. An important property of tumours closely related to angiogenesis, is tumour hypoxia [9, 10]. Tumour hypoxia is associated with resistance to chemo- [11] and radiation therapy [12], and selection for the most resilient tumour cells [13]. Hypoxia stimulates tumour angiogenesis which subsequently relieves the hypoxic region and facilitates prolific growth. As the tumour grows the cells become further separated from the vasculature which induces another state of hypoxia where the tumour is dormant until angiogenesis resumes. Hypoxia is a clinically relevant parameter as it reduces the effects of chemo- and radiotherapy; prevents drug delivery to non-vascularised hypoxic regions and influences cell-cycle specific chemotherapies [14]. The study of hypoxia as a predecessor to angiogenesis provides additional relevant information on tumour heterogeneity and periodicity. UCNPs have been engineered as oxygen sensing complexes [15, 16] and microcirculatory imaging can indicate regions of low perfusion. A

detailed reconstruction of physiological processes like hypoxia and angiogenesis will aid in understanding tumour-specific behaviour, and give insight into cellular processes.

The combination of tumour diagnostics and therapy, theranostics, is exemplified by UCNP-mediated photodynamic therapy (PDT). In PDT, cancer cells are destroyed through the generation of cytotoxic singlet oxygen by molecules that act as photosensitizers when excited by optical irradiation. By selecting photosensitizers that absorb in the emission bands of UCNPs, powerful complexes can be generated by loading UCNPs with many photosensitizers. Exciting the UCNP-PDT complexes by 980 nm light results in the generation of singlet oxygen and detectable emission via the green and red UCNP emission bands respectively [17]. Tumour drug delivery of UCNP-PDT nanocomplexes provides novel mechanisms for therapy and diagnostics [18]. The presence of the drug can be confirmed by detection of UCNPs in the tumour, while the effect of therapy on the tumour vasculature post-treatment (assessed by laser speckle flowmetry) is instrumental to evaluate the impact of therapy.

A recognized problem for the delivery of drugs to tumours is the elevated interstitial pressure in the tumour core [19], which dramatically hampers perfusion rates of the core tumour vessels. The perfusion rate and extravasation of nanoparticles are possibly interrelated which can be assessed by the combination of flowmetry and quantification of nanoparticle delivery. In addition, some tumour therapies are aimed at inhibiting uncontrolled angiogenesis in order to normalise the tumour vessels, resulting in a reduced interstitial pressure and an increased delivery of drugs [20]. The combination of both techniques is extremely helpful in monitoring the intended effects of these experimental therapies.

In this last chapter I have described potential collaborations between quantitative perfusion and photoluminescence imaging. The combined application of both techniques can intensify the information on the complex interaction of tumour cellular processes, tumour growth, metastasis and tumour response to therapy.

9.3 REFERENCES

1. C. A. Den Uil, E. Klijn, W. K. Lagrand, J. J. Brugts, C. Ince, P. E. Spronk, and M. L. Simoons, "The microcirculation in health and critical disease," *Progress in cardiovascular diseases* **51**, 161-170 (2008).
2. B. Fagrell and M. Intaglietta, "Microcirculation: its significance in clinical and molecular medicine," *Journal of internal medicine* **241**, 349-362 (1997).
3. W. D. Strain, D. D. Adingupu, and A. C. Shore, "Microcirculation on a large scale: techniques, tactics and relevance of studying the microcirculation in larger population samples," *Microcirculation* **19**, 37-46 (2011).
4. R. Weissleder, "A clearer vision for *in vivo* imaging," *Nature biotechnology* **19**, 316-316 (2001).
5. G. Chen, H. Qiu, P. N. Prasad, and X. Chen, "Upconversion Nanoparticles: Design, Nanochemistry, and Applications in Theranostics," *Chemical reviews* (2014).
6. J. V. Frangioni, "*In vivo* near-infrared fluorescence imaging," *Current opinion in chemical biology* **7**, 626-634 (2003).
7. P. Carmeliet and R. K. Jain, "Angiogenesis in cancer and other diseases," *nature* **407**, 249-257 (2000).
8. J. Folkman, "Angiogenesis in cancer, vascular, rheumatoid and other disease," *Nature medicine* **1**, 27-30 (1995).
9. M. Höckel and P. Vaupel, "Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects," *Journal of the National Cancer Institute* **93**, 266-276 (2001).
10. A. Facciabene, X. Peng, I. S. Hagemann, K. Balint, A. Barchetti, L.-P. Wang, P. A. Gimotty, C. B. Gilks, P. Lal, and L. Zhang, "Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and Treg cells," *nature* **475**, 226-230 (2011).
11. L. I. Cárdenas-Navía, T. W. Secomb, and M. W. Dewhirst, "Effects of fluctuating oxygenation on tirapazamine efficacy: theoretical predictions," *International Journal of Radiation Oncology* Biology* Physics* **67**, 581-586 (2007).
12. L. B. Harrison, M. Chadha, R. J. Hill, K. Hu, and D. Shasha, "Impact of tumor hypoxia and anemia on radiation therapy outcomes," *The Oncologist* **7**, 492-508 (2002).
13. R. Welsh, F. Jensen, N. Cooper, M. Oldstone, B. Banapour, J. Sernatiriger, J. Levy, H. Hoshino, H. Tanaka, and M. Miwa, "Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours," *nature* **379**, 4 (1996).
14. M. A. Shah and G. K. Schwartz, "Cell Cycle-mediated drug resistance an emerging concept in cancer therapy," *Clinical Cancer Research* **7**, 2168-2181 (2001).
15. L. Liu, B. Li, R. Qin, H. Zhao, X. Ren, and Z. Su, "Synthesis and characterization of new bifunctional nanocomposites possessing upconversion and oxygen-sensing properties," *Nanotechnology* **21**, 285701 (2010).
16. D. E. Achatz, R. J. Meier, L. H. Fischer, and O. S. Wolfbeis, "Luminescent sensing of oxygen using a quenchable probe and upconverting nanoparticles," *Angewandte Chemie International Edition* **50**, 260-263 (2011).
17. K. Liu, X. Liu, Q. Zeng, Y. Zhang, L. Tu, T. Liu, X. Kong, Y. Wang, F. Cao, and S. A. Lambrechts, "Covalently assembled NIR nanoplatfor for simultaneous fluorescence imaging and photodynamic therapy of cancer cells," *Acs Nano* **6**, 4054-4062 (2012).
18. N. M. Idris, M. K. Gnanasammandhan, J. Zhang, P. C. Ho, R. Mahendran, and Y. Zhang, "*In vivo* photodynamic therapy using upconversion nanoparticles as remote-controlled nanotransducers," *Nature medicine* **18**, 1580-1585 (2012).
19. C.-H. Heldin, K. Rubin, K. Pietras, and A. Östman, "High interstitial fluid pressure—an obstacle in cancer therapy," *Nature Reviews Cancer* **4**, 806-813 (2004).
20. U. Prabhakar, H. Maeda, R. K. Jain, E. M. Sevick-Muraca, W. Zamboni, O. C. Farokhzad, S. T. Barry, A. Gabizon, P. Grodzinski, and D. C. Blakey, "Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology," *Cancer research* **73**, 2412-2417 (2013).