



# Melanin Fluorescence as a Bridge in the Theranostics of Malignant Melanomas

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## Article Info

### Article Notes

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Melanin, as a skin pigment, is both a natural protection against UV radiation and the vehicle for malignant transformation into melanoma (black skin cancer). This dual function has earned it the nickname “two-edged sword.”

Melanin is produced in pigmented skin cells (melanocytes). Its protective function is based on melanin’s characteristic light absorption, which increases exponentially from the near-infrared through the visible spectrum to the ultraviolet. The malignant transformation process (melanomagenesis) proceeds via two different pathways<sup>1</sup>: in approximately 70-80% of cases, melanoma cells arise directly from melanocytes; these form so-called *de novo* melanomas. A second pathway of melanomagenesis occurs via nevi. These are clusters of melanocytes that have undergone cellular changes. These healthy nevi can transform into dysplastic nevi (with various atypical features). Here, further development diverges: dysplastic nevi can become malignant melanomas (nevus-associated melanoma) or - like normal nevi - progress to the senescence stage. Finally, some of these senescence nevi may even regress, i.e., disappear, later in life (involution stage). The aforementioned differences in melanoma development depend on body site (more nevus-associated lesions on the trunk of younger patients) and on melanoma subtype (superficial spreading melanoma is most often nevus-associated; nodular, lentigo maligna, and acral lentiginous melanomas are usually *de novo*).

The diversity of this pigmentation, and especially malignant transformation, can be clearly characterized by its varying melanin fluorescence<sup>2,3</sup>. This is of high diagnostic value. It is all the more remarkable because melanin is considered non-fluorescent, with a fluorescence quantum yield of  $10^{-4}$ , and is overexposed by the fluorescence of other endogenous pigments when excited conventionally<sup>3</sup>. However, this melanin fluorescence can be measured using a special technique of nonlinear laser spectroscopy: Fluorescence is stimulated by the stepwise absorption of two photons from an 800 nm nanosecond laser. These photons are not absorbed by the other skin pigments, and the melanin reaches the fluorescent level with the energy of two of these photons. The fluorescence generated in this way shows significant spectral differences depending on whether it originates from normal melanocytes, melanoma cells, or benign or atypical nevus cells. In particular, melanoma cells exhibit a specific (red) fluorescence. This is a clear diagnostic indicator of melanoma, both *in vivo*<sup>3</sup> and in histological preparations<sup>3,4</sup>. Melanoma fluorescence thus represents

an essential complement to the gold standard of melanoma diagnostics, histological examination, as an objective criterion for melanoma diagnosis.

The molecular mechanism of this red melanoma fluorescence is currently unknown.

The method is called dermatofluoroscopy and can be performed using a dermatofluoroscope<sup>3, 5</sup>. With this instrument, suspect melanocytic lesions *in vivo* can be investigated in a scanning mode, sampling and analyzing the fluorescence from a dense grid of measuring points, each representing a skin area with a diameter of 30 micrometers. From the distribution of these typically several hundred spectra, a resulting diagnosis for the entire lesion is derived using a scoring system. It indicates benign nevus, melanoma, or a more or less dysplastic nevus. In the latter case, periodic follow-up examinations at intervals of a few months are recommended. In such follow-up examinations over several years, all the stages and progressions listed above have been observed: from slightly suspicious nevus to dysplastic nevi to melanoma\*; most frequently to the state of senescence, but also progressions from benign nevi to the final stage, involution. (\* During a follow-up examination with an increasing score in the dysplastic nevus stage, the patient is advised to undergo excision; in very rare cases, this was refused, and subsequently a melanoma *in situ* developed.)

Dermatofluoroscopy has been tested in clinical use<sup>5, 6</sup>.

Recent studies have shown that the specific red melanoma fluorescence is linked to hypoxia in the surrounding tissue<sup>7</sup>. Tumor hypoxia is an important micro-environmental factor that influences, and can be targeted by, cancer therapies<sup>8</sup>.

Fluorescence-based diagnostic detection of a skin area with malignant melanocytic transformation thus simultaneously identifies the site of therapeutic intervention (theranostics). It is possible to start microtherapy at the very beginning of a malignant transformation as can be identified through melanin fluorescence follow-up monitoring. Such microtherapy techniques are currently a rapidly developing field of research<sup>9</sup>.

In this context, particular attention is being paid to photodynamic therapy (PDT). Classic PDT was ineffective against melanoma largely because melanin both blocks activating light and quenches oxygen-derived radicals; the additional problem of tumor hypoxia has now been quantified and is a key focus of modern PDT research. New photosensitizers, oxygen-supplying nano-materials, and combination regimens are being investigated<sup>10, 11</sup>.

Just as fluorescence spectroscopic follow-up in case of incipient malignant transformation indicates the starting area for therapeutic intervention, future studies must

clarify whether the initiation of successful therapy leads to a return to the fluorescence of benign melanocytic lesions.

It is noteworthy that the same characteristic red melanin fluorescence also occurs in choroidal melanoma<sup>12</sup>, despite the different tissue specificity in the uveal tract of the eye. Red melanin fluorescence also occurs in pigmented basal cell carcinoma<sup>5</sup>, thus it also serves here as an indicator of malignancy and a marker for the site of potential therapeutic intervention. It would be desirable to make the highly informative but extremely weak melanin fluorescence commercially available *in vivo* and in histological preparations, the regulatory requirements for the medical market have been met.

Finally, it should be noted that neuromelanin, which is structurally related to melanin, also exhibits red fluorescence. Neuromelanin is located in the pigmented part of the human midbrain where hypoxia and Parkinson's disease mechanisms are linked<sup>13-15</sup>. Theranostics of Parkinson's disease would be highly desirable, but is still some way off. In summary, the red fluorescence of melanin and neuromelanin is an exciting area of research.

## Conflicts of Interest

There are no conflicts of interest.

## References

1. Jackett LA, Scolyer RA. Review of Key Biological and Molecular Events Underpinning Transformation of Melanocytes to Primary and Metastatic Melanoma. *Cancers* 2019, 11, 2041 doi: 10.3390/cancers11122041.
2. Leupold D, Scholz M, Stankovic G, et al. The stepwise two-photon excited melanin fluorescence is a unique diagnostic tool for the detection of malignant transformation in melanocytes. *Pigment Cell Melanoma Res.* 2011 Jun; 24(3): 438-45. doi: 10.1111/j.1755-148X.2011.00853.x.
3. Leupold D, Pfeifer L, Hofmann M, et al. From Melanocytes to Melanoma Cells: Characterization of the Malignant Transformation by Four Distinctly Different Melanin Fluorescence Spectra (Review) *Int. J. Mol. Sci.* 2021;22:5265. doi: 10.3390/ijms22105265.
4. Leupold D. Fluoreszenzbasierte Melanomdiagnostik. Eine flankierende objektive Methode zur Dermatohistologie. *Dermatologie.* 2023; 74: 725-729. doi: 10.1007/s00105-023-05182-x.
5. Forschner A, Keim U, Hofmann M, et al. Diagnostic accuracy of dermatofluoroscopy in cutaneous melanoma detection: Results of a prospective multicentre clinical study in 476 pigmented lesions. *Br. J. Dermatol.* 2018, 179, 478-485. doi: 10.1111/bjd.16565.
6. Szyć Ł, Hillen U, Scharlach C, et al. Diagnostic Performance of a Support Vector Machine for Dermatofluoroscopic Melanoma Recognition: The Results of the Retrospective Clinical Study on 214 Pigmented Skin Lesions. *Diagnostics (Basel).* 2019 Aug 25; 9(3): 103. doi: 10.3390/diagnostics9030103. PMID: 31450697.
7. Leupold D, Buder S, Pfeifer L, et al. New Aspects Regarding the Fluorescence Spectra of Melanin and Neuromelanin in Pigmented Human Tissue Concerning Hypoxia. *Int J Mol Sci.* 2024 Aug 2; 25(15): 8457. doi: 10.3390/ijms25158457.
8. Jeon S, Jeon M, Choi S, et al. Hypoxia in Skin Cancer: Molecular Basis and Clinical Implications *Int J Mol Sci.* 2023 Feb 23; 24(5): 4430. doi: 10.3390/ijms24054430.

9. Zhou L, Xu S, Li S. Microneedle-Mediated Transdermal Drug Delivery for the Treatment of Multiple Skin Diseases. *Pharmaceutics* **2025**, 17, 1281. doi: 10.3390/pharmaceutics17101281.
10. Zhan Q, Mu J, Shi X, et al. Oxygen-evolving hollow polydopamine alleviates tumour hypoxia for enhancing photodynamic therapy in cancer treatment. *Nanoscale Adv* . 2022 Oct 19; 4(23): 5021-5026. doi: 10.1039/d2na00549b.
11. Obalola AA, Abrahamse H, Dhilip Kumar SS. 3D-printed biopolymer-based microneedle for enhanced photodynamic therapy in melanoma treatment. Review *Front Oncol*. 2025 Sep 17; 15: 1642448. doi: 10.3389/fonc.2025.1642448. eCollection 2025. PMID: 41040513.
12. Schneider M, Teuchner K, Leupold D. Two-photon fluorescence of ocular melanomas. *Studies on a new diagnostic method. Zweiphotonen-Fluoreszenz okularer melanome. Studien zu einer neuen diagnostischen Methode. Ophthalmologie* 2005, 102, 703-707. doi: 10.1007/s00347-004-1171-5.
13. Leupold D, Szyk L, Stankovic G, et al. Melanin and Neuromelanin fluorescence studies, focusing on Parkinson's disease and its inherent risk for melanoma. *Cells* 2019, 8, 592. *Cells*. 2019 Jun 15; 8(6): 592. doi: 10.3390/cells8060592.
14. Leupold D, Buder S, Pfeifer L, et al. New Aspects Regarding the Fluorescence Spectra of Melanin and Neuromelanin in Pigmented Human Tissue Concerning Hypoxia. *Int J Mol Sci*. 2024 Aug 2; 25(15): 8457. doi: 10.3390/ijms25158457.
15. Ye Q, Wen Y, Al-Kuwari N, et al. Association Between Parkinson's Disease and Melanoma: Putting the Pieces Together. *Front. Aging Neurosci*. 2020; 12: 60. doi: 10.3389/fnagi.2020.00060.