NL Agency
Ministry of Economic Affairs

Project number: IPD12004
Project name: Development of a Raman spectroscopic device for the objective assessment of pigmented skin lesions (RASKIN)
Goal: to develop a low-cost, easy-to-use Raman spectroscopic device for dermatologists and primary-care physicians for a rapid and objective identification of suspicious pigmented skin lesions

Early diagnostics of skin cancer with Raman spectroscopy

Melanoma is the most lethal form of skin cancer. Early diagnostics is crucial as it significantly enhances the patient-survival rate. However, the clinical diagnosis of early-stage melanoma remains difficult. The IOP project 'RASKIN' aims to develop a prototype of a low-cost, easy-to-use photonic device that will help dermatologists and primary-care physicians identify suspicious, pigmented skin lesions. The project will also deliver an extensive set of clinical data to verify the effectiveness of the instrument.

Worldwide, the number of patients diagnosed with melanoma is increasing by 4% each year. An estimated 6,000 cases are expected in the Netherlands alone in 2015. While early diagnostics could make a real difference for patients, the clinical diagnosis of early-stage melanoma is difficult even for the most experienced dermatologists. Most assessments are currently made on the basis of visual inspection and are thus highly subjective. Suspicious pigmented skin lesions are then surgically removed and examined by a pathologist. As it is hard to distinguish between malignant and benign tissue, many skin samples are unnecessarily removed for examination, while at the same time a substantial number of early-stage melanomas go unnoticed. Those could very well metastasize to distant organs. As metastatic melanoma is resistant to chemotherapy, the prognosis for patients who have it is very poor: the median survival time is no more than a few months. "It is therefore of the utmost importance to be able to diagnose melanoma accurately at a very early stage, before deadly metastasis has occurred," says Marijn Sandtke, business consultant at TNO. "We have high hopes that we can achieve this with the help of a generic technology called Raman spectroscopy."

"Using a Raman spectroscopic device, sample tissue no longer has to be surgically removed"

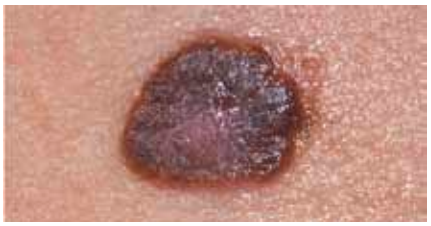
Fingerprint

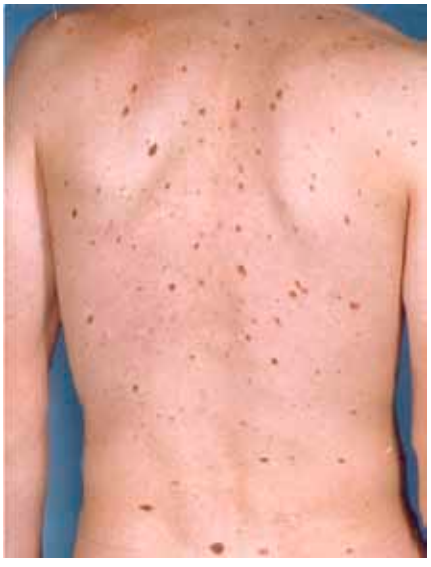
Using a Raman spectroscopic device – Raman spectroscopy was named after the Indian scientist Sir C. V. Raman – sample tissue no longer has to be surgically removed, but merely illuminated with a laser beam. "When laser light reflects on the molecules in the sample, it causes vibrations and rotations of the atoms in the molecules within the illuminated spot," Sandtke explains. "By measuring the differences in the energy levels between the entering and exiting photons, it is possible to determine which molecules are involved. In this way, we can establish the (bio)molecular composition – the signature – of pigmented skin lesions. Since the signatures of melanoma and benign tissue are quite different, this type of analysis would greatly enhance the clinical diagnosis of melanoma in an early stage."

In a previous project, TNO successfully used the Raman technique ex-vivo on liver-tumour tissue. Using it on melanoma presents some difficulties, however. As they are dark brown or even almost black in colour, this type of tissue absorbs most of the laser light, resulting in both an unwanted heating of the tissue and poor signals. Fluorescence is another serious problem. Not only do the molecules in the sample absorb the laser light, but they also generate a strong background signal that makes it harder to detect the molecular fingerprint. By using infrared laser light, this IOP project hopes to circumvent both problems. This type of light – with a wavelength of approximately 1,000 nm – reduces both absorption and the generation of unwanted background fluorescence.

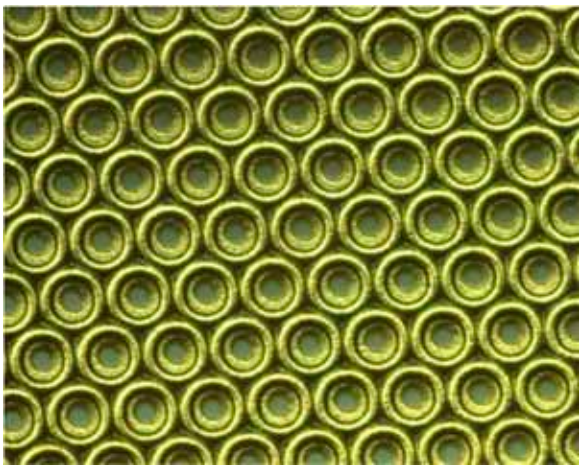
Handheld unit

To develop a photonic device based on infrared Raman spectroscopy, it will be necessary to develop a number of technologies beyond the current state of the art. This will happen during the first two years of the project. "The first technology is the laser itself," says Sandtke. "We will need a compact, low-cost infrared laser with high wavelength

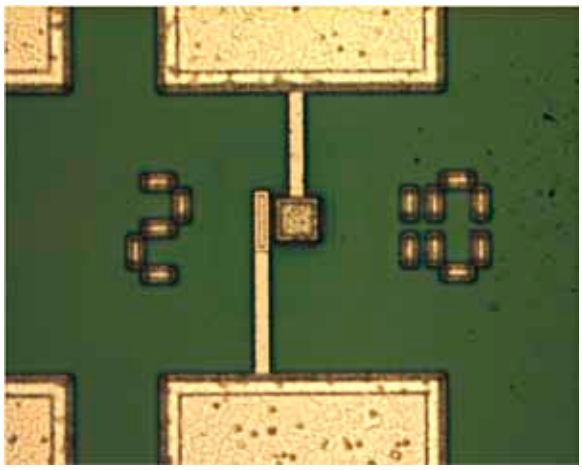




The back of a patient, containing dozens of pigmented skin lesions ('moles') (Source: LUMC)



An array of vertical-cavity surface-emitting lasers (VCSEL), which will be used in the Raman spectroscopic device (Source: Philips Lighting)



Example of a photodiode detector connected to two metal pads. The size of the detector is 10×10 μm2 (Source: Delft University of Technology)

stability. Our project partner Philips Lighting will work on this part of the project." The second technology that needs improvement is the detector. The Delft University of Technology will further develop an existing photodiode process to produce a detector with a sufficiently low noise level (1 kHz dark count rate) for this application. "TNO will be responsible for the opto-mechanical design of both the spectrometer and a handheld measurement unit that can be used by dermatologists and primary-care physicians. This so-called collection probe will need to be able to focus the laser light at the correct position and collect the signals from the lesion. It also needs to be light, small and ergonomic. Erasmus MC – which initiated the project – will help us define the specifications for the spectrometer, probe, laser and detector. For the spectrometer, we can build on TNO's long history of designing infrared spectrometers for space applications." Yet another project partner, Avantes, will incorporate the various techniques into a working prototype.

Data collection

Developing the Raman spectroscopic device is one thing; correctly distinguishing between malignant and benign tissue is another. Sandtke: "To enable the interpretation of the tissue-sample signatures, the Center for Optical Diagnostics and Therapy at Erasmus MC will develop the necessary algorithms. During the last year and a half of the project, once the prototype has become available, clinical data will be collected and tested in order to improve those algorithms." Data collection will take place at the Department of Dermatology at the Leiden University Medical Center. This hospital is the Netherlands' national centre for skin oncology and has the largest pigmented lesion clinic in the country. "There we can compare the results of the Raman device with those from pathological evaluation. At that stage of the project we will also decide on how to present the data from the device to dermatologists and physicians. Will it be enough to show them the test results in green, orange or red, or would they prefer numbers or a graph? By 2016, after having tested the prototype extensively within the Department of Dermatology, we will have a prototype of which both the accuracy and the sensitivity will be known."

Participants:

- TNO
- Delft University of Technology
- Erasmus MC
- Avantes
- Philips Lighting
- Leiden University Medical Center

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