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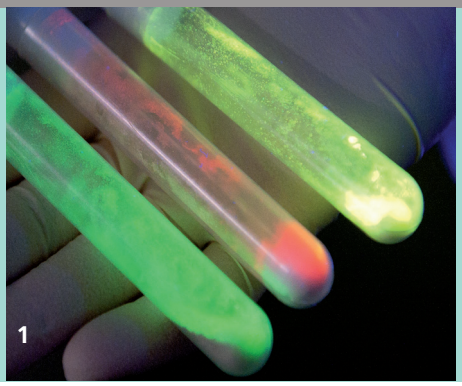

1/2 *Nanoparticles are labelled with a luminescent dye in order to obtain visual proof of the successful binding of an antibody.*

MULTIFUNCTIONAL NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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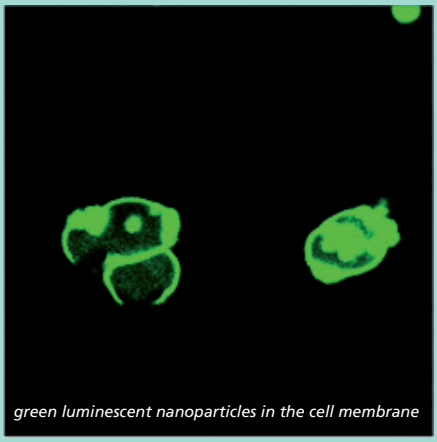
Cancer and cardiovascular diseases are still the most frequent cause of mortality in Germany and Europe. And yet the prospects of survival are relatively high in both cases, on condition that the disease is diagnosed in good time.

One way to enable a more timely diagnosis involves the detection of molecular markers that are present in a patient's blood serum. If methods were improved to detect markers in extremely low concentrations, patients could receive their personalized therapies at a far earlier stage.

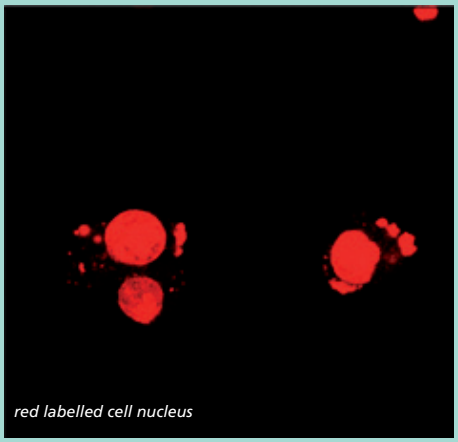
These issues are tackled by the collaborative research project IMIKRID (Integrated microfluidic diagnostic systems), which is funded by BMBF within the scope of the »Integrated microsystems for biotechnological applications« development program. The aim of the preliminary research project is to create a technology platform for the development of an integrated microfluidic diagnostic system. Alongside other detection methods, the aim is to integrate a significantly more sensitive form of antibody-based biomarker analysis in a diagnostic chip, thus enabling the creation of extremely compact, portable and modular diagnostic systems capable of supplying clinically relevant measurement results within a matter of minutes.

All-round concept for early diagnosis

Biochemical markers in blood serum also play a major part in the diagnosis of cancer and cardiovascular diseases. Current serological tumor marker tests have a detection limit of 10-11 mol/l. One of the goals of IMIKRID is to develop a multi-sensor system capable of simultaneously detecting relevant tumor-specific and cardiological markers while also offering a portable capacity



green luminescent nanoparticles in the cell membrane



red labelled cell nucleus

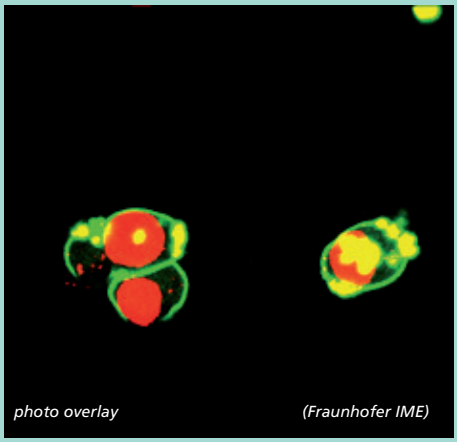
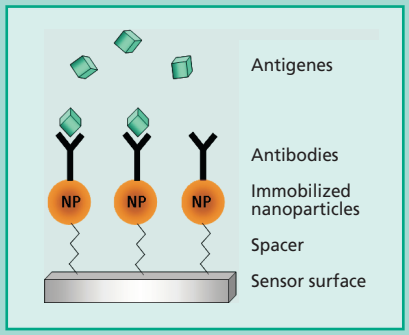


photo overlay *(Fraunhofer IME)*

for early serological tumor diagnosis and the prevention of cardiovascular diseases.

The core component of the overall system is a microfluidic chip equipped with microchannels through which a blood sample is circulated. The goal is to employ antibody-antigen reactions to measure even the smallest concentration of disease-specific markers in the blood serum in vitro and to achieve a 100-fold improvement over the detection accuracy offered by current state-of-the-art methods. This opens up the possibility of detecting diseases earlier and improving patients' chances of recovery.



Multifunctional SiO_2-based nanoparticles enable the conjugation of marker-specific antibodies or relevant antigens and are tailored to both the sensor system and the microfluidics of the diagnostic system.

Multifunctional nanoparticles

As part of the project, the Fraunhofer ISC is developing the fundamental component of this detection system: multifunctional dye-doped SiO_2-based nanoparticles. These act as a binding partner for the antibodies/antigens and help to amplify the signal in a fluid environment. The key factors here are the size, shape and surface of the nanoparticles, since these are the geometric parameters that determine the type and quantity of antigens that can subsequently be captured and the level of precision that can be achieved when measuring marker concentrations in the microfluidic system. Synthesis of SiO_2 particles (d = 60-200 nm) is conducted by sol-gel technology. Covalent binding of the fluorophore molecules to the inorganic SiO_2 matrix prevents the dye from leaking out of the particle and increases the resistance to photobleaching.

Fluorophore-labelled particles also open up the option of using an optical sensor system. The particles are modified with entities of varying reactivity such as carboxyl and amino groups, for example. These functions facilitate the targeted coupling of antibodies to the particle surface. The reaction of the particle-bound antibodies with the antigen causes a change in the charge on the particle surface, which is registered by the sensor chip.

In addition, the nanoparticles are being specifically adapted to the particular requirements of the microfluidic system, with a spacer being used to position the nanoparticles in the middle of the particle stream in order to increase the sensitivity of the microfluidic diagnostic system.

First successful results

Over the last year, individual modules of the integrated microfluidic diagnostic system have undergone successful testing. The Fraunhofer ISC supplied the newly developed luminescent and surface-modified nanoparticles to the Fraunhofer IME, where a variety of different antibodies and antibody fragments were bound to the nanoparticles. The functionality of the bound antibodies was verified by subsequent biological tests. It was demonstrated that the antibodies remain active and, as intended, are able to bind various biomarker antigens. The coupling of the nanoparticles to the sensor chip is still being tested.

Project details

IMIKRID – Integrierte mikrofluidische Diagnostiksysteme (Integrated microfluidic diagnostic systems) supported by the Federal Ministry of Education and Research (BMBF)
ID W3BIO057
Project duration:
September 2006 to November 2009
Project partners:
Fraunhofer FIT, St. Augustin
Fraunhofer IME, Aachen
Fraunhofer IMS, Duisburg
Fraunhofer ILT, Aachen
Fraunhofer ISC, Würzburg
CIS Institut für Mikrosensorik GmbH, Erfurt