A medical laboratory in your wallet

Medicine for the future

Biochips are revolutionizing diagnostics technology

At present, diagnostic tests are mainly carried out in large-scale laboratories and the patient only gets the results a few days later. Scientists at Bayer Technology Services are working on the development of miniaturized laboratories that will soon allow general practitioners to diagnose genetic abnormalities, diseases or the patient's general state of health within a matter of minutes.

The medical laboratory of the future has no windows or doors and no one goes in or out – although that wouldn't be possible anyway, as it is so small that it would fit into your trouser pocket. On an area the size of a credit card, it can perform tests which in the past needed several hundred square meters of laboratory space. Scientists at Bayer Technology Services are developing these miniature analytical devices for Bayer HealthCare's Diagnostics Division. These biochips – also known as the lab-on-a-chip – are tools designed to enable new, more individualized treatment and as such are regarded as the most promising development in medical diagnostics. Soon, typical tests could be moved from large central laboratories right into the doctor's surgery,

Dr. Ingmar Dorn (l.) and Dr. Kerstin Bohmann check the laser lens system for fluorescence measurement.

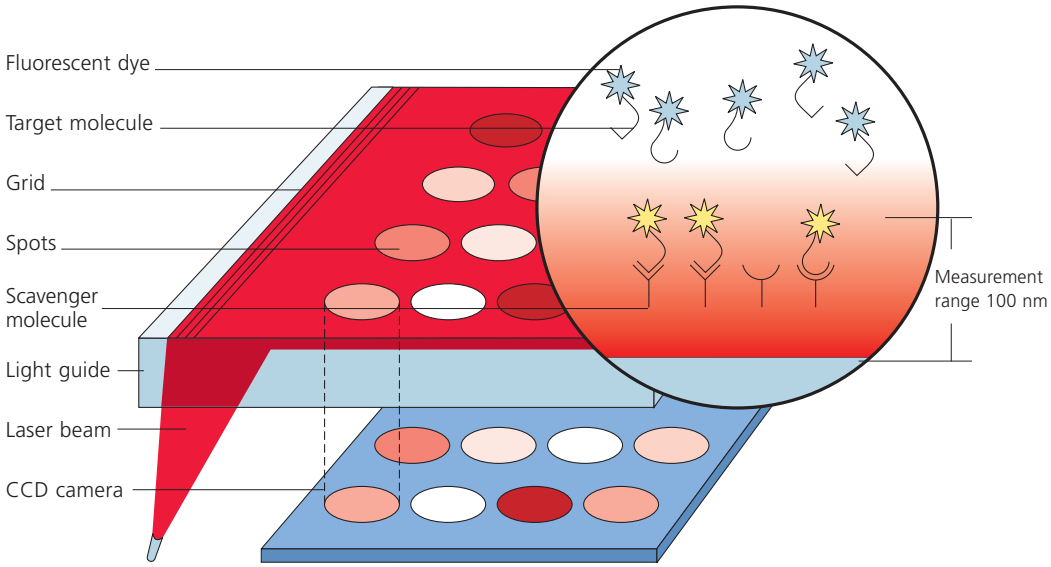
thus helping to find the best possible treatment for each individual patient. "Patients react to medicines in very different ways," says Dr. Christoph Petry, who works in Diagnostics Research at Bayer HealthCare in Germany.

Microfluidics on the biochip replace large-scale laboratories

Miniaturized analytical devices have two distinct advantages over the large-scale equipment used in today's diagnostic laboratories: they are considerably cheaper – making them affordable for a general practice – and they will be as easy to use as a test strip, making specially trained staff superfluous.

This new type of diagnosis is made possible by the rapid developments in molecular biology and advances in the miniaturization of parts required for detection techniques. The term lab-on-a-chip was coined in the 1990s. "Of fundamental importance with this technology is the fact that it is possible to handle small sample quantities in a very confined space," says Dr. Ingmar Dorn of the Biophysics Competence Center at Bayer Technology Services in Leverkusen. "Microfluidics", as this technology is known, uses a simple law of nature: as the dimensions of an object change, so too do its physical properties. For example, capillary action draws the sample of a fluid such as blood fully automatically along narrow channels, from where it is taken to a mixing container, precisely metered, mixed with reagents and labeled with, for example, a fluorescent dye. Heating elements regulate its temperature precisely and valves and pumps control its distribution. The giant sets of apparatus typical of a large laboratory are rendered partly superfluous by this technology.

The subsequent analysis of the sample takes place at the heart of the miniature laboratory, on the biochip: a small glass plate a few square centimeters in size that was built by the scientists at Bayer Technology Services. On this glass plate, for example, blood can be tested for changes to the genotype or for the presence of certain proteins that tend to occur in increased quantities in diseases. Each test is carried out on a



Scavenging action on the biochip
The DNA is separated into individual fragments and marked with a fluorescent dye, either by a chemical reaction or by means of another recognition sequence.
The sample fluid is applied to the surface of the chip and scavenger molecules (in the individual spots) filter out target molecules (special gene sequences or a certain protein). Only these target molecules bind to the "scavenger arms". A laser is used to illuminate the grid and planar waveguide technology and a special camera are employed to measure the fluorescence in a very thin layer directly on the surface of the chip.

"spot" on the chip surface that has a diameter of 100 micrometers. There is sufficient space on a one square centimeter chip for several hundred spots, and hence also for several hundred measurements at the same time. As little as 50 to 100 microliters of blood – i.e. only a few drops – are enough for Bayer scientists to carry out their analyses.
Each spot contains biomolecules that can identify a specific gene sequence or a specific protein from the sample fluid. "These scavenger molecules are printed on to the surface of the chips like letters in an inkjet printer," explains Dorn. For the "scavenging action" the scientists use either small pieces of DNA (deoxyribonucleic acid = the carrier of genetic information) – which act as counterparts to the gene segments being sought – or antibodies which bind to special proteins.

The concept of the test is simple: the blood sample is applied to the analysis spots on the surface of the chip. If it contains the gene sequences or proteins being sought, they accumulate at the spot concerned. The fluorescent dye which is bound to one of the biomolecules involved in the reaction shows that this accumulation has taken place. A special measuring instrument evaluates the result.
What sounds so simple is not so easy to put into practice technically, because although the dye attaches to the bound molecules on the chip surface, it also floats freely in the sample fluid, thereby creating additional signals which make a clear diagnosis difficult. The remaining dye therefore has to be first removed in several washing steps – a major disadvantage, as errors can occur as a result of each additional step.

To overcome these problems, the experts at Bayer Technology Services employed a new fluorescence measurement technique called planar waveguide technology. This process uses a physical effect to measure the fluorescence in only a thin layer 100 nanometers thick directly on the surface of the chip, where the binding of the biomolecules takes place. This not only makes the additional washing steps unnecessary, but because it does away with the false signals from the unbound dye, the new method can provide measurements which are 20 to 100 times more sensitive than those produced with comparable fluorescence methods. For example, the procedure can detect the minutest amounts of less than an attomole (10^{-18} mole) of DNA in blood.

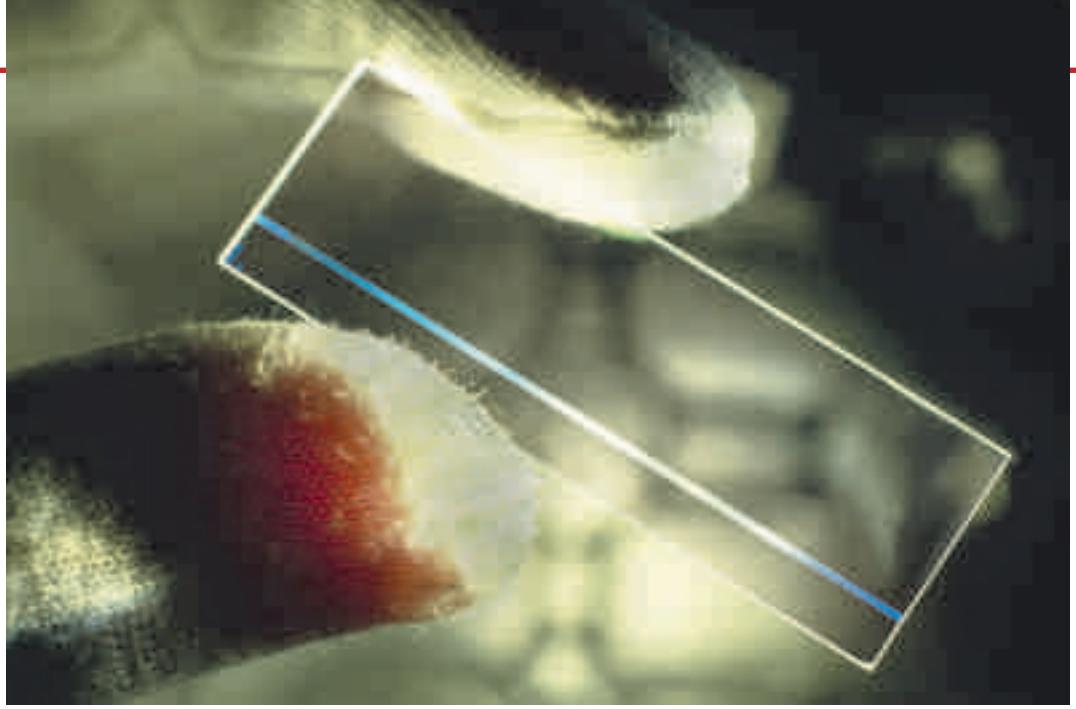
Novel fluorescence measurement for reliable diagnosis

Dorn and Petry are working together on the development of biochips and fluorescence measurement: within four to five years, it should be possible to use the chips for a wide variety of applications in medical diagnosis. The ultimate goal on which the two researchers and their team have set their sights is individualized treatment based on the analysis of a patient's genotype. This will allow the best possible medi-

DNA chips – beyond diagnostics

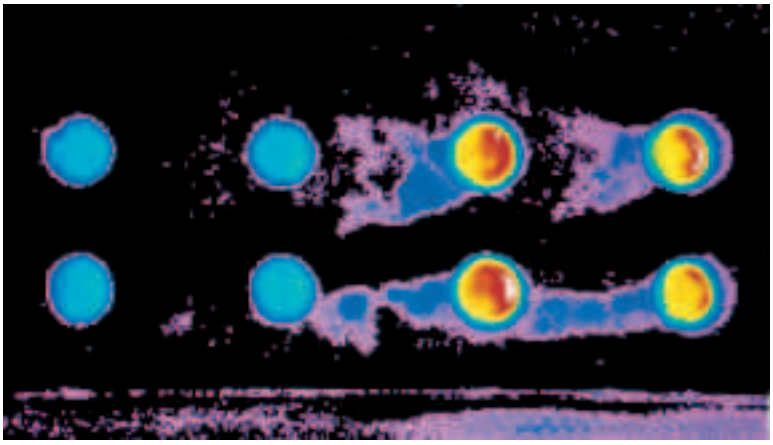
In addition to medical diagnosis, the lab-on-a-chip technology will also have a major role to play in other applications in future.

Examples of applications	Purpose
Drug development	Targeted and rapid design of new active ingredients
Cancer research	Identification of cancer genes and individual risks
Microbiology	Classification of microorganisms
Food industry	Analysis of various disease pathogens in food



Laser beams make the nanostructures of the biochip mini-laboratory visible to the naked eye.

The measurements are displayed on the screen as color-coded dot patterns.



cine to be found, suited to the peculiarities of each individual patient, and will help to avoid adverse effects.

"The cause of different reactions to a drug product – and the associated side effects – are what are known as SNPs in our genes," explains Petry. These "single nucleotide polymorphisms" are quasi point mutations – a substitution of individual bases in the DNA. Each human being has three million such invisible mutations. They are the main reason why individuals differ from one another. "It has been known for some years that some of these SNPs affect the way in which medicinal products work – for example, because they affect a gene which is responsible for breaking down the active ingredient in the liver," says Petry. The scientists want to analyze these mutations using biochips. In fact, genetic testing is already being used today to check the suitability of medicinal products. "But up to now there has been no procedure which allows this analysis to be carried out in the space of a few minutes in the doctor's surgery," continues Petry. What's more, the scientific data needed for such applications are not available for most drug products. The possibilities for the use of these have therefore been limited up to now.

"Genetic tests could also make the search for the ideal treatment of carcinomas such as breast cancer easier," says Petry. This is because there are a great many forms that respond to medicines in completely different ways. One reason for this can be found in genetic mutations. Many types of tumor contain proteins, for example, as a result of such genetic mutations, which flush out an active ingredient from the cell before it can take effect. Others react to a medicinal product which blocks their energy metabolism by switching to another form of energy generation – i.e. the tumor becomes resistant. Initially, researchers want to identify as many such resistance mechanisms for different drug products as possible. Once these are known, it could be possible to identify the most promising active ingredient before treatment of the tumor begins. "A few dozen such tests would be sufficient for genetic characterization," Petry says.

http://faculty.washington.edu/yagerp/microfluidicstutorial/tutorialhome.htm
This website contains detailed information on microfluidics.