

Search for active substances to combat serious cardiovascular disease

Help for weak hearts



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Targets

Cardiac cell cultures: to ensure that there is enough material for testing, cardiac cells are cultivated (right). Dr. Ulrich Nielsch (above) analyses the genes of the cells. The background shows the graphic evaluation of a gene chip experiment. Each dot corresponds to an individual gene. The colors show the strength of genetic activity in each case.



There are many drug products available for the treatment of heart failure, but none of them actually get to the core of the problem. Bayer scientists are aiming to change this. An active substance which protects heart muscle cells is currently at the development stage. Molecular biology testing of heart tissue from patients suffering from heart failure set them on the right track.



Many keys to success are initially rather unprepossessing. For example the pea-sized reddish tissue samples that Bayer HealthCare's Dr. Peter Ellinghaus takes out of the freezer. "These samples could open the way to new drug products to combat a deadly disease," he explains. A 34-strong group at Bayer HealthCare's Target Research Institute in Wuppertal, Germany, is searching for new drug products to combat heart failure. This is not just another compound in a long series of established active substances. "We want to establish an entirely new therapeutic principle," explains the head of the institute, Dr. Ulrich Nielsch, "and finally get to the root of the problem."

There are about five million patients with heart failure in the United States and about ten million in Europe. The reason that the figures are so high is that heart failure is the final stage of several cardiovascular diseases. The starting point is always damage to the heart muscle. In about half of all cases it is caused by a heart attack, in about a third high blood pressure contributes to the disease and more rarely, infections are the trigger.

Those affected have a worse chance of survival than many cancer patients. About half die within five years of diagnosis. This is because the heart usually becomes weaker and weaker. It's a vicious circle: when the heart muscle is unable to pump strongly enough, the body uses various messen-

ger substances to try to increase blood pressure, heart rate and the strength of the heartbeat. This only puts more pressure on the already weakened heart muscle, however. Nowadays, doctors can use drugs to slow down this ultimately fatal counter-reaction (see box on page 48).

The search starts with heart tissue

"However, the cascade of destruction in the heart muscle gradually continues," explains Nielsch. The body is only able to replace dead heart muscle cells with useless scar tissue. The remaining muscle cells, however, are stretched under the increasing workload, the heart expands to twice or three times its original size and so loses more strength. In addition, more connective tissue develops between the cells; an accompanying inflammatory reaction in the heart can further weaken the force with which it pumps. The heart muscle cells are often also enlarged, further reducing the output. "Myocardial remodeling" is what the doctor calls this. "So far, no-one has got to the bottom of these changes," says Nielsch with regret. "We still don't know which biochemical processes nor which genes are involved."

His team is looking for a remedy. The key is to conduct molecular biology tests on the heart tissue of patients with heart failure. Such sample mate-



Gene chip test: Ina Flocke prepares the gene chip scanner which can analyze up to 48 chip experiments overnight (right). Beforehand, the chips are cleaned in a washer system to remove dye reagents (left).

Help against the fatal downward spiral

Drug products are now available which can slow down the progression of chronic heart failure and prolong survival. However, no active substance is as yet available that can combat pathogenic changes to the heart.

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| ACE inhibitors | Reduce blood pressure and prevent the formation of angiotensin II, a messenger substance which raises blood pressure. |
| Angiotensin II receptor blockers | Prevent angiotensin II from binding to its receptor sites. |
| Beta blockers | Lower blood pressure and heart rate via the sympathetic nervous |
| Cardiac glycosides | Stabilize and strengthen the heart beat. |
| Diuretics | Reduce blood volume and blood pressure and alleviate edema. |
| Heart transplants | Implantation of a healthy heart from a donor. |
| Implantable defibrillators | Neutralize fatal arrhythmias. |
| Left ventricular assist devices | Cardiac pumps, temporary alternative to transplants. |
| Spironolactone | Occupies the binding sites for aldosterone, a hormone that regulates blood pressure and is produced excessively by heart patients. |

rial is rare, however: "Autopsy samples taken long after death are of no use, as the messenger RNA which we need to analyze has long since decomposed," explains Ellinghaus. An especially tragic situation does provide an option, however: for many patients, a transplant is the only hope when the disease has progressed to a certain stage. Just 398 heart transplants were carried out in Germany in 2005 - not enough to meet even half the country's needs and the

situation is similar in other countries. The reason for this is a constant decline in organ donors. In order to tide emergency cases over the waiting period, doctors are more and more often implanting mechanical pumps as left ventricular assist devices. When they are implanted and later when the transplant is carried out, there is always some heart muscle tissue left over. Sometimes the patient's heart has even recovered slightly by the time the

transplant is carried out. As part of a co-operative research project with Professor Reiner Körfer, private lecturer Dr. Hendrik Milting and Dr. Aly El Banayosy of the North Rhine-Westphalia Diabetes Center in Bad Oeynhausen, the Bayer scientists obtained such tissue samples from 32 patients before and after mechanical circulatory back-up implanting.

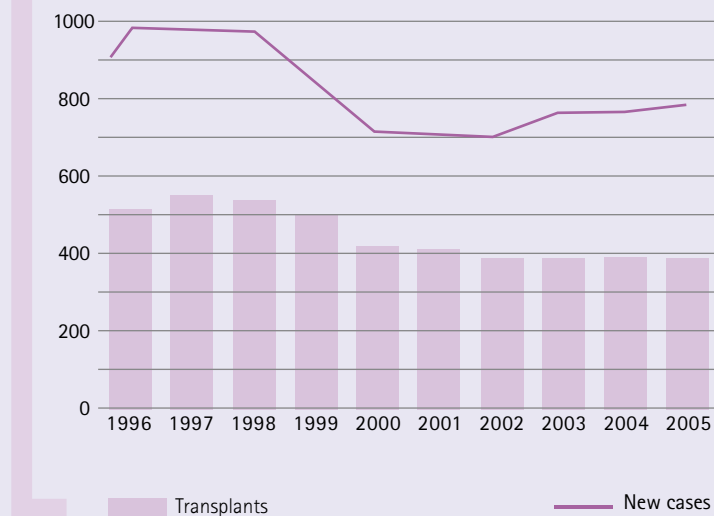
Hundreds of genes in sick hearts lose the beat

In the critical analysis, the scientists compare which genes are active in the various heart muscle samples and hence the protein content of the muscle cells. This is because proteins which are found in different quantities in the "before" and "after" samples may be associated with the progression of the disease and could serve as targets for pharmaceutically active substances.

An indicator of the activity of a gene is the quantity of messenger RNA (mRNA) it forms, which serves as a blueprint for protein production. The RNA is first purified from the samples



New cases of heart failure and heart transplants



Enormous need
As the example of Germany shows, the number of new cases far outweighs the number of transplants. Patients on the waiting list can sometimes be helped with a heart pump. When these pumps are implanted, tiny pieces of heart muscle have to be removed. These are examined by Bayer researchers in their search for new targets.

and then analyzed on a gene chip. A gene chip carries all human genes as probes on thousands of individual points. Only when RNA molecules bind to the appropriate site for them is a signal created, the intensity of which provides information on the concentration of RNA in the sample currently being examined.

Finally, the PC determines the regulated genes in a tissue sample from the data which have been scanned in. The outcome: about 100 genes in the myocardial cells of patients are disease-dependently regulated.

"We can't develop new treatments for hundreds of potential targets all at the same time," says Nielsch. "We have to be selective." Target candidates are given bonus points, for example, if they are part of a genetic family which has already been the subject of pharmacological research.

This is why a special protein which is located on the surface of heart muscle cells, biochemically known as a G protein-coupled receptor, came out on top in the Bayer scientists' search for targets. There is already a great deal of

pharmacological experience with these receptors: hundreds of drug products act on the body through other representatives of this large receptor family. "For the next tests, we were therefore able to refer back to reference compounds which also target this receptor, but which had been developed for other indications," says Nielsch. The cardiovascular function of this special receptor is still unknown. "We are assuming that it is directly involved in the pathological process, as it is found almost exclusively on the heart muscle cells of heart failure patients," he adds in explanation.

New therapeutic approaches for heart patients

Further evidence was provided by rats with heart failure which, when given the reference compound which blocks this receptor, showed much less pathological thickening of the heart muscle. Researchers are currently screening Bayer's own large compound library for inhibitory substances which have a favorable pharmacological profile.

Research with these will be pursued to develop a new drug product especially for the treatment of heart failure.

However, it will be some years before such a product is on the market. The first steps have been taken, though. Nielsch is convinced that "genes which are overactive in patients' hearts also contain the central cause of the disease. Hopefully, we can use them to find possible approaches for new, more effective treatments." Genetic research is getting ready to solve the puzzle of heart failure.



www.heartfailure-europe.com

The Cardiovascular Research Foundation provides a readily understandable explanation of heart failure.