PIPETTE ROBOTS ARE USED IN PREPARING FOR LARGE-SCALE SCREENING. PHOTO: T. SCHWERDT/DKFZ

German Cancer Research Center

DRAGNET INVESTIGATION IN THE GENOME

The robot arm whirs quietly as it aims precisely for the 384 dimples in a plastic plate and inserts minute quantities of various reagents. More than 200 of these plates pass through the fully automated stations from preparation to partially automated microscopic evaluation. “We are carrying out a kind of dragnet investigation of the human genome,” smiles Professor Michael Boutros, head of the department of Signalling and Functional Genomics at the German Cancer Research Center. “We are looking for genes which play an important part in cancer.”

> “We are conducting a genome-wide search for suspicious genes.”

In the current project, Heidelberg researchers around Michael Boutros are collaborating with Professor Georg Halder and colleagues from the M.D Anderson Cancer Center in Houston, Texas, to detect genes whose activity is responsible for the survival of cancer cells. The two groups’ experience complement each other perfectly: the Boutros laboratory has established the large-scale screening process while the colleagues at M.D. Anderson Cancer Center have wide experience in developing and testing active ingredients. In the “hunt” for the genes, Boutros uses the RNA interference (RNAi) as a screening method. This method uses short double-stranded RNA molecules which suppress certain gene sequences and thus inhibit the production of proteins within the cell. In their experiment, the researchers expose cancer cells and normal cells under identical conditions to the effects of gene-specific RNAi samples. If the cancer cells die while normal cells survive, this could indicate the presence of one of the genes they are looking for. “We are conducting a genome-wide search for suspicious genes,” says Michael Boutros, “in other words, hunting for a needle in a haystack.” Without large-scale screening, it would not be possible to cope with the task of examining 25,000 genes and many times that number of RNAi samples, hence the large amount of time and effort spent by Boutros and his working group developing and establishing the large-scale RNAi screening.

> “We may discover genes which permit an entirely new approach to cancer treatment.”

To test automatically how cells behave after the genes have been suppressed, they have also developed special microscopy processes which enable thousands of images to be taken and analysed. All data are collected and entered into a database which is widely used internationally. They also make their experience and infrastructure available to other researchers. Michael Boutros explains that they almost always have several visiting researchers who study their methods and then apply them to their own projects. The Heidelberg scientist ran an international EMBO course on large-scale RNAi screening in June 2008. In the first screening phase, the Boutros laboratory often uses Drosophila fruit fly cells. “Drosophila mostly lack functional redundancy, so that the suppression of a gene has immediately visible effects,” Michael Boutros explains. “This is an advantage if you want to prove loss of function.” This makes the system so well suited to finding prospective candidates among the genes whose relevance must of course then be tested in further experiments. Using this strategy, the Heidelberg-based researchers have already found several interesting genes, including Evi, identified in Drosophila; a gene which intervenes in the signalling pathways of cell differentiation and tumour formation. Experiments show that Evi has an important signalling function in human cells too.
Human cancer cell strains are used in the second screening phase. Established active ingredients and new ones still in the experimental stage are tested to find genes whose suppres-

sion increases the effectiveness of cancer medication. Michael Boutros and his scientific team anticipate findings which lead to a more focused cancer therapy, for example, which chemotherapeutic medicine could be best used for patients with a particular genetic disposition. Looking to the future, Michael Boutros envisages perhaps discovering genes which permit an entirely new approach to cancer treatment.

HELMUTH PROKOPH

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TITIN – TRACKING AN ALL-ROUNDER AND ITS FUNCTIONS

Titin is the largest protein in the human body and is located in the sarcomere, the molecular unit of the muscle fibres in the musculoskeletal system and the heart. It creates an elastic link between parts of the sarcomere, which move towards each other as the muscle contracts and return to their original position when the muscle is at rest. Professor Michael Gotthardt and his working group at the Max Delbrueck Center in Berlin are collaborating with colleagues from the University of Arizona and Washington State University to examine the functions of titin in the context of biomechanics, metabolism and signalling pathways. They hope that their research will reveal more about the causes of heart disease and amyotrophy. The titin molecule is made up of 26,000 parts grouped in functional modules. In order to gain an idea of the functions of the

> Michael Gotthardt's working group has produced the first titin-based animal model for diastolic cardiac insufficiency, which is especially prevalent in women.

various modules, the Gotthardt laboratory has produced mice whose heart muscles produce titin with altered modules. Either a particular module does not function from the start or its production can be switched off. Through these experiments, the researchers have established that titin has many regulatory functions. For example, if the N2B module is switched off, the mouse develops a smaller heart with less elasticity.
Michael Gotthardt and his group of researchers have produced a strain of N2B-KO mice, the first titin-based animal model for diastolic cardiac insufficiency, which is especially prevalent in women. Molecular mechanisms which lead to cardiac insufficiency can be examined using this model; researchers hope that this will enable them to develop new treatment strategies.

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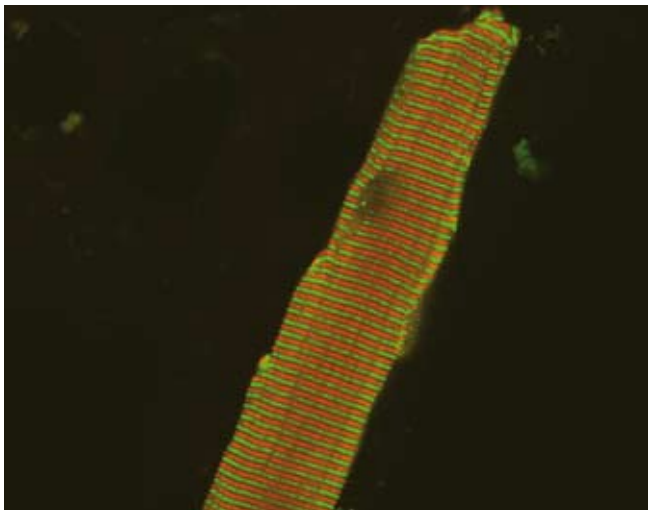

ISOLATED MOUSE CARDIAC CELL. THE STRIPES ARE CAUSED BY THE REGULAR ARRANGEMENT OF THE PROTEINS ACTININ (RED) AND TITIN (GREEN). Photo: Michael Radtke, MDC