Hessian Ministry
of Economics, Transport, Urban and Regional Development

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HESSEN

# Personalised Medicine in Hessen

## New Technologies for Customised Therapies

Hessen – there´s no way around us.

Hessen Biotech

# „Hessen has a tradition as a pharmaceutical region“

**Five questions to Florian Rentsch,**

**Hessian Minister of Economics, Transport, Urban and Regional Development**

***Minister, personalised medicine is a still relatively young segment in the pharmaceuticals market. What opportunities do you think it will open up for society?***

Rentsch: In view of the country's aging population, the prevention, early recognition and specific treatment of widespread diseases take on greater importance. Personalised medicine is opening up interesting new approaches here. More accurate diagnoses and corresponding individualised therapies have great medical and economic potential. Personalised medicine promises not only chances for better and more rapid healing; it also provides an opportunity to cut the costs of treatment, thus reducing the burdens on the health system. More accurate diagnoses can help to avoid side effects and the high costs involved by the necessary follow-up treatments. In this way personalised medicine will bring benefits not only for physicians and patients but also for the health system as a whole.

***What is the economic potential?***

Rentsch: There is no doubt that personalised medicine is a growth market. Up to the present time personalised medicine rests on 20 drugs, a number which is expected to increase rapidly. Experts reckon with global growth rates of around 12 percent per year. However, this will call for a great deal of research and development. With its pharmaceutical sector, Hessen is in an excellent position in this respect. Already now, researchers and industry are successfully providing new impulses, due to the fact that the highly innovative research activities of biotech and pharmaceutical companies go hand in hand with top academic research.

What is more, the value chain in pharmaceutical research and development will undergo major changes. The diagnostic sector, which is already in a strong position in Hessen, will grow further still. The cooperation between small biotech firms and major pharmaceutical companies will become increasingly important. In contrast to standard health care, there will probably be no more blockbuster drugs with billions in turnover as in the past.

***You mentioned the leading position of Hessen as a pharmaceutical location. What is the reason for this success?***

Rentsch: Hessen has a tradition as a pharmaceutical region. The entire process chain is represented here. Companies and research facilities pursue their activities in an innovative environment. At an early date Hessen recognised biotechnology as a growth driver and set up Hessen Biotech as a point of contact. Personalised medicine as a special area of biotechnology benefits from this infrastructure. The networks already established in Hessen are yet another advantage. Personalised medicine can draw on reliable and experienced structures such as our successful cluster initiatives. One very good example is CI3, the Rhine-Main Cluster for Individualised Immune Intervention, which has set itself the goal of making the region a global leader in individualised immunotherapeutics against cancer and rheumatic disorders, with the support of strong partners from Hessen. Half of all the partners from science and industry are from Hessen.

Photo: HA Hessen-Agentur GmbH

**Personalised Medicine in Hessen**

New Technologies

for Customised Therapies

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**of the Aktionslinie Hessen-Biotech**

***That sounds as though this is all a matter for the giants of the sector. Will it mean disadvantages for the SMEs which are such a characteristic feature of Hessen as an industrial and scientific region?***

Rentsch: On the contrary. What counts in innovative sectors is interdisciplinary cooperation. There is an observable trend for major concerns in particular to engage more frequently in cooperations with small firms and universities. The capital of SMEs is their specialisation. They often possess a specific know-how, a particular competence, which the larger companies depend on. Another characteristic feature of SMEs is their high flexibility – an asset when it comes to putting new knowledge quickly into practice. The universities make their scientific expertise available. With their basic research and interdisciplinary research projects they make valuable contributions to the network.

***Is personalised medicine from your point of view an element of Hessen's innovation and growth strategy?***

Rentsch: Quite definitely yes. Hessen has always been open for new ideas. Change has tradition here. Hessen provides an environment in which promising new sectors can grow from old roots, because it has a favourable climate for innovation. This – in addition to its central location, its excellent infrastructure and its highly qualified human resources – is what gives Hessen its particular quality. Personalised medicine holds a great deal of potential which it can develop in Hessen.

# Content

# The Way to Personalised Medicine

***Physicians have at all times endeavoured to tailor medical treatment to the needs of the individual patient. To do this, they relied on established parameters such as body weight and blood pressure.***

For a long time, however, limits were set to further individualisation – too little was known about the reasons why one and the same diagnosed disease could take many very different courses, or why drugs worked for one patient but not for another. For many diseases there are even nowadays no therapies which help all patients. Even modern drugs often fail to show the desired effect. In the case of psychopharmaceuticals, for instance, it can often take up to one year to find the right drug in the right dose. Moreover – "no effects without side-effects" – the administration of drugs involves risks.

In fact, it is estimated that about 17,000 deaths every year in Germany are due to side-effects. This means that if side-effects could be reduced, human lives could be saved. The causes of individual differences in reaction are located in the genes, but until a few years ago it was technically impossible to find them. The situation has been changed by the development of chip-based methods. The time and costs needed to identify disease-triggering variants in the genetic material are being constantly reduced. This has opened the way to searches for "biomarkers" –

## 1866

**The Catholic priest Johann Gregor Mendel publishes rules by which traits are inherited in peas.**

## 1879

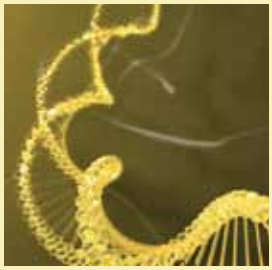
**Walther Flemming describes the "chromatin" in the cell nucleus, later to be identified as the hereditary material DNA.**

## 1902

**The British physician Archibald Garrod studies metabolic disorders and observes that they are inherited in families. He realises that the laws of inheritance also apply to human beings and assumes that hereditary factors form the basis of the "chemical individuality" of human beings.**

## 1913

**Thomas Hunt Morgan recognises further laws of inheritance in his experiments with the fruit fly "Drosophila melanogaster".**



## 1953

**James Watson and Francis Crick publish a helical model for DNA.**

i.e. particular cellular markers specific to a disease and the course it takes. With their aid it is also possible to identify sites of action in and on the cells for which new drugs can be specifically developed.

Photo: Universität Frankfurt am Main

***"Personalised medicine offers many advantages for patients by allowing them to be treated more gently and effectively. Non-responders need not be submitted to useless therapies, and the costs for treatment of side-effects can be avoided."***

**Prof. Theodor Dingermann, Institute for Pharmaceutical Biology, University of Frankfurt am Main, and Official Biotechnology Representative of the State of Hessen**

## 1959

**Friedrich Vogel coins the term "pharmacogenetics" for the study of how drugs are influenced by differences in the genetic make-up of patients.**

## 1961

**Research groups work on decoding the genetic code.**

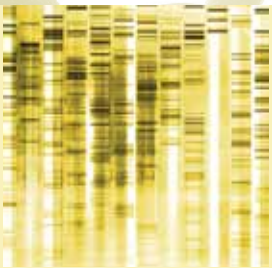
## 1994

**The first commercially available DNA chip comes on the market (HIV).**

Photo: Sanofi-Aventis

## 1998

**Herceptin® is approved by the U.S. Food and Drug Administration (FDA), together with the HER2 diagnostic test to identify the target group.**



## 2003

**The sequencing of the human genome is finally completed after 13 years and investments of three billion US dollars.**

## ...2015

**The sequencing of the complete genome will probably become available for less than 1,000 euros.**

**80%**

**Up to 80 percent of patients are non-responders to certain drugs, which means that, because their genetic profile, they are unable to benefit from a particular drug at the recommended dose or may even be at risk from it.**

# From Disease to Therapy

***Diseases vary just as much as individual persons. This fact draws attention to two distinct levels which must be taken into account for the personalised treatment of patients: the diseases themselves, and the patients with their genetic make-up.***

Photo: Universitätsklinik Frankfurt am Main

***"Personalised medicine has already reached the patient in cancer therapy. We no longer administer the same drug to all patients but use specific drugs which attack particular tumour cell structures."***

**Prof. Manfred Kaufmann, Director of the Department of Gynaecology and Obstetrics at the University Hospital in Frankfurt am Main**

## Personalisation of diseases

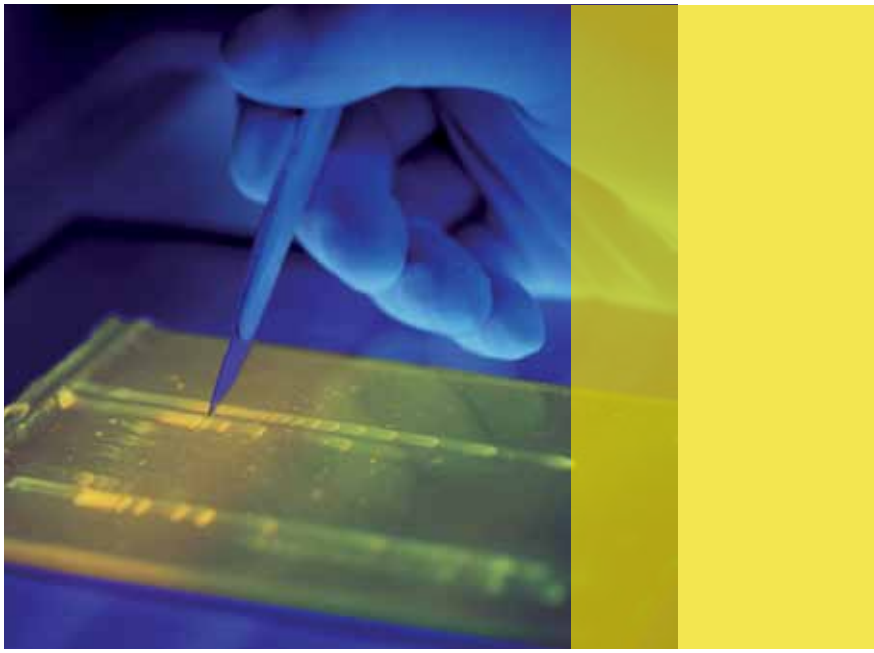
Therapy nowadays for various types of cancers no longer takes the form of a physical or chemical barrage fire directed indiscriminately at all dividing cells but attacks the tumour cell itself. Certain targets which are located predominantly on these tumour cells (such as growth receptors on the cell surfaces) are blocked by highly specific drugs. One such target, e.g. in the case of breast cancer, is the co-called HER2 receptor, which is specifically blocked by the drug trastuzumab (Herceptin®). This has the effect of preventing tumour growth.

However, only about 20 percent of women affected by breast cancer have this receptor present in quantities sufficient to make the treatment really effective. Before the start of Herceptin® therapy, therefore, evidence must be obtained to show that it is effective. Other kinds of breast cancer cells respond to therapies such as oestrogen deprivation. For this reason, the breast cancer subtype is first determined in specialised centres before a start is made on personalised therapy.

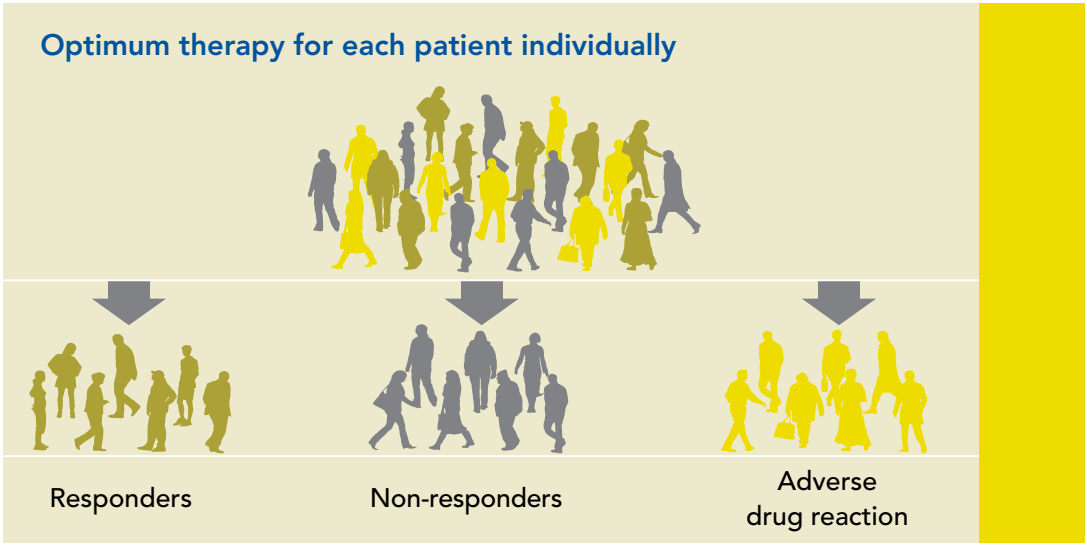
## Personalisation of the patient

Depending on the class of drug in question, individual active ingredients are for up to 70 percent of the patients either without effect or have such marked side-effects that the therapy has to be discontinued. This is due to the individual metabolism, which determines whether one and the same concentration of a drug is too high and thus produces side-effects, or too low and thus has no therapeutic effect. It is these individual differences which decide whether persons react to a medicament or not, i.e. whether they are responders or non-responders. How an individual person's metabolism functions is determined genetically.

The still relatively young discipline of pharmacogenetics characterises differences in metabolism and uses them for predicting the therapeutic efficacy of the drug or the risk that it will produce adverse effects. In this way it becomes possible to select a suitable drug in the correct dose.



**How metabolism functions is genetically determined**




Source: Johann Wolfgang Goethe-Universität, Frankfurt am Main

Photo: Merck KGaA

**804**

**Manufacturers made a turnover of 804 million euros in Germany alone with drugs requiring a companion diagnostic test.**

# Where do we stand today?
# The Status Quo

***Much is being said about personalised medicine in the future, but even now it has become firmly established in branches of medicine such as oncology and virology.***

The life expectancy of HIV patients nowadays is almost as high as that of the normal population. This has become possible because the drug cocktail is adjusted regularly to each individual patient's particular disease course. In cancer therapy, too, there are an increasing number of indications where individualised attacks are directed at tumour cell structures which are present in only some of the patients. At the present time approvals have been granted in Germany to 18 active ingredients which are used in conjunction with a companion diagnostic test.

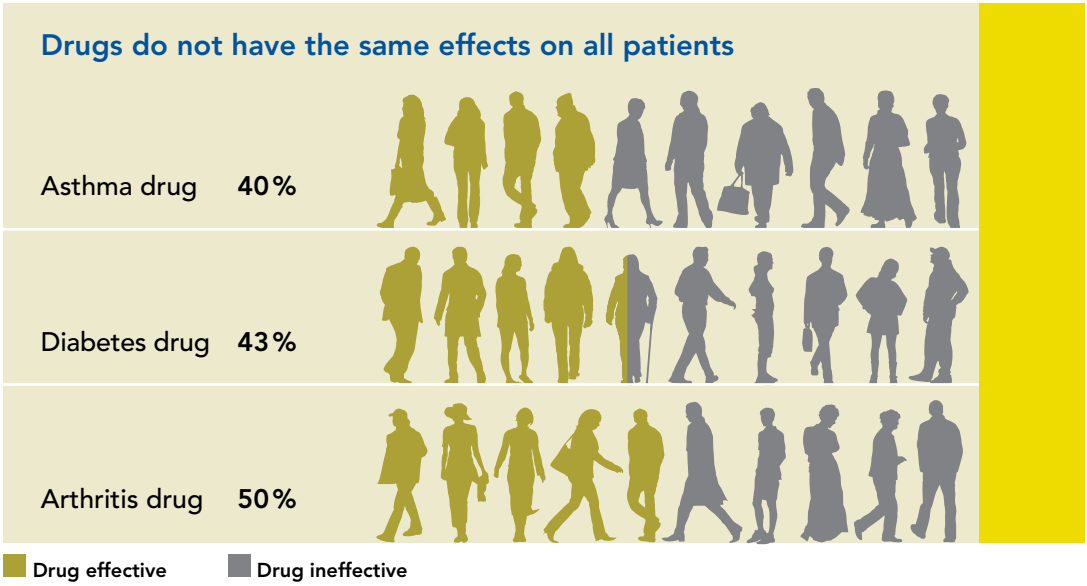
Oncology is an area in which personalised medicine has arrived in everyday practice, but there are other branches of medicine where this is not yet the case. But even here the interest in personalised medicine is great. Intensive research is being carried out into ways of applying personalised treatment e.g. for disorders of the central nervous system (such as Alzheimer's disease) or the metabolic disease diabetes. To this end scientists are focusing their attention on the identification and characterisation of new biomarkers as a basis for new therapies.

## 18 active ingredients with diagnostic test approved in Germany

| | |
|---|---|
| **Abacavir*** | **HIV/AIDS** |
| **Anastrozol** | **breast cancer** |
| **Azathioprin*** | **immunosuppressant** |
| **Cetuximab** | **intestinal cancer, head/neck tumours** |
| **Dasatinib** | **acute lymphatic leukaemia** |
| **Exemestan** | **breast cancer** |
| **Fulvestrant** | **breast cancer** |
| **Gefitinib** | **lung cancer** |
| **Imatinib** | **certain types of leukaemia** |
| **Lapatinib** | **breast cancer** |
| **Letrozol** | **breast cancer** |
| **Maraviroc** | **HIV/AIDS** |
| **Mercaptopurin*** | **oncology** |
| **Nilotinib** | **chronic myelod leukaemia** |
| **Panitumumab** | **intestinal cancer** |
| **Tamoxifen** | **breast cancer** |
| **Toremifen** | **breast cancer, stomach cancer** |
| **Trastuzumab** | **breast cancer, stomach cancer** |

* Only as test for adverse drug reactions

Status as at April 2011




Source: Ernst & Young, Personalized Medicine Coalition, May 2009

## A change of thinking in the pharmaceutical industry

The search for such biomarkers is laborious, and to make it more efficient pharmaceutical companies have begun to change their business strategies. Large concerns are cooperating more and more frequently with research institutions and biotech firms in order to cut down time and costs. One example of this is the public private partnership between Sanofi-Aventis and the Charité University Medicine Berlin. The aim of the active partners in this cooperation is to make joint use of their R&D know-how so that patients can benefit sooner from new drugs for personalised therapies of strokes or of inflammatory autoimmune diseases such as rheumatoid arthritis.

Even rival pharmaceutical giants are moving closer together. Merck KGaA in Darmstadt is planning joint research with Sanofi-Aventis U.S. on active ingredient combinations to block specific signal pathways in cancer cells. These combinations – one active ingredient from Merck with two from Sanofi-Aventis – are being tested for safety and efficacy in initial human studies.

The combination of diagnostics and therapy points the way to successful personalised medicine – as is shown by the example of Hoffmann-La Roche, where research into, and development of, new medicaments and diagnostic products has been brought together under one roof. The systematic linking of the two business divisions was declared to be corporate strategy as early as 2006.

Photo: vfa

***"There are already several diseases for which personalised medicine is helping to find the therapies best suited to individual patients and to make more efficient use of health budgets. In the future the list of such diseases will certainly become longer."***

**Dr. Siegfried Throm, Executive Director of Research at the German Association of Research-Based Pharmaceutical Companies (vfa)**

50%

**Over 50 percent of all biotech companies in Hessen conduct research and development of their own. This is the basis for personalised medicine.**

# Research and the Market – Hessen in Focus

***Without biomarkers there can be no personalised medicine – and without tests for these markers it will be impossible to predict success. If we have no parameters for assigning patients to particular groups (stratification), it will be impossible to find and implement therapies optimally tailored to their needs.***

The aim of modern research in personalised medicine is to discover biomarkers of this kind and develop new drugs to match them. Biomarkers have a part to play throughout the entire process of a personalised medical treatment – from recognition of the disease (diagnostic markers) to prediction of the probable course of the disease (prognostic markers) to selection of the right therapy in the form of medication and dosing. This process chain is flanked by risk research into the origins of diseases and into the sites of action for new drugs.

It thus becomes immediately apparent that personalised medicine revolves around tests for the presence of particular biomarkers and their characteristics. This is a field where Hessen's biotech firms are frequently at the forefront.

Yet another point emerges clearly: since research and therapy cover such a wide range of activities, the success of personalised medicine will depend on interdisciplinarity. The discovery of important markers and new active ingredients together with further clinical development can only be achieved by intensive networking of experts in basic and clinical research at university research institutes or in pharmaceutical and biotechnology companies.

Hessen – and more especially the Rhine-Main region with its long pharmaceutical tradition – is making a major contribution to the development of personalised medicine along the whole of process chain. Leading biotechnology players are domiciled here. And, as is so often the case in highly specialised fields, it is not only the major pharmaceutical concerns which are contributing to value creation but also very largely the small and medium-sized biotech companies.

# Biomarker Tests – the Basis of Individual Therapy

## Putting biomarkers to clinical use

***Will a selected active ingredient produce the desired effect? If this question can be answered in advance, time and money – and often a great deal of suffering – could be saved.***

One company working on this highly relevant task is Targos GmbH in Kassel, which for this purpose has linked up research, development and clinical activities. With its biomarker tests it contributes to the development of active ingredients and diagnostic products, thus helping to increase the success rate of therapies.

The company, though still young, has already achieved considerable success, and last year it set up two subsidiaries, Targos Development AG and Targo Advance AG. It played a part in the registration of five personalised medicine therapies in the USA and Europe, and also of seven biomarkers (in vitro diagnostics, IVD). Over 30,000 patients have been analysed by the company in more than 60 studies conducted worldwide. With its knowledge and experience in tissue pathology and molecular biology, the company is making an important contribution towards furthering the registration of personalised drugs and diagnostic products. Major concerns such as Hoffmann-La Roche have been working together with Targos for years on the development of personalised medicine. The fact that the Swiss concern, which is itself actively engaged in pharmaceutical and diagnostic research, has looked for support in Hessen serves to underline the importance of Hessen's achievements on the way to personalised medicine.

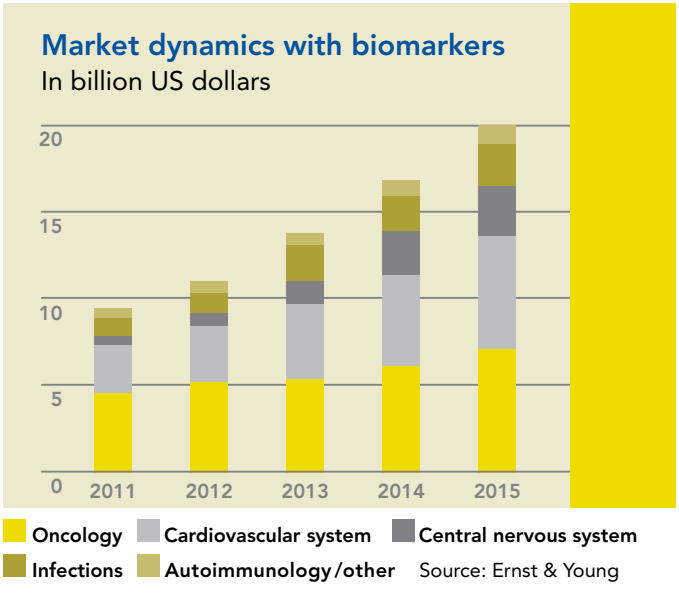
Photo: TARGOS Molecular Pathology GmbH

***"Our responsibility does not end with the development of innovative diagnostic and therapeutic tests. With our training programmes we also ensure that they are put to correct clinical and practical use – only then will the results be right."***

**Dr. Thomas Henkel, CEO of TARGOS Molecular Pathology GmbH, Kassel**

Targos sees its role as an overall service provider and partner. Biomarker tests may be developed and approved, but their application in practice still has to be learnt. When such tests do not run fully automatically and their evaluation is difficult, user training becomes particularly important. Targo offers training for users in clinics and medical practices, thus speeding up the use of the test in daily clinical routine and ensuring that scientific progress is made available for the benefit of the patients.

**Market dynamics with biomarkers**
In billion US dollars



# The energy supply makes all the difference

***ScheBo Biotech AG in Giessen makes simultaneous use of biomarkers for personalised medicine in several areas. The company sets its focus on something which tumour cells in many different types of cancers have in common – their energy metabolism.***

The energy supply of cancer cells is different from that of healthy cells. The key enzyme of this modified metabolic pathway bears the name M2-PK. A test system developed by the company is able to quantify the enzyme in blood samples, thus making it possible to test the efficacy of therapies for a great variety of different cancers – and at the same to distinguish between responders and non-responders. However, the test systems from ScheBo Biotech are useful not only for persons who are already ill. The company also provides a system for detecting M2-PK in stool samples, thus allowing preventive examinations for intestinal cancer to be carried out non-invasively. And a test used for checking pancreatic function has developed worldwide into the leading diagnostic marker for non-invasive pancreas testing.

Photo: ScheBo Biotech AG

***"We are in a position to use tumour metabolism to test the efficacy of cancer therapies. We put the same knowledge to use for the development of new active ingredients and potential new drugs."***

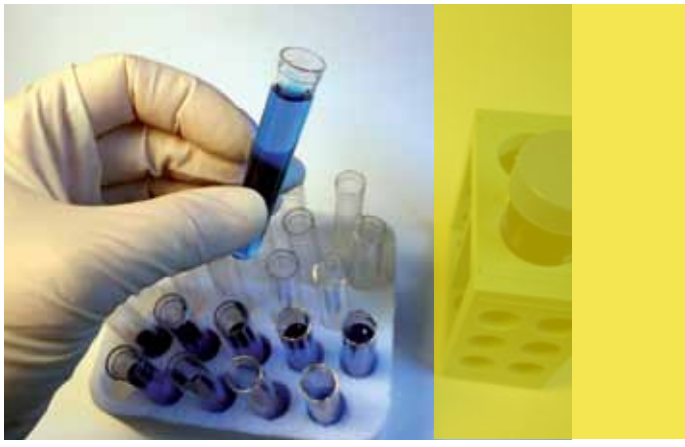
**Dr. Ursula Scheefers-Borchel, Board of Executives of ScheBo Biotech AG, Giessen**

Another aim of research at ScheBo is the determination of so-called therapeutic "targets". The company, which also owns subsidiaries in the USA and Great Britain, has identified new targets and is at present developing corresponding active ingredients for potential new drugs. Several active ingredients are already in the pipeline. The next step will be to enter into cooperations with pharmaceutical concerns, since the clinical development of the candidate active ingredients calls for large-scale studies which can only be performed jointly with major companies.

# Solutions also for on the spot decisions

***Central Hessen is growing in importance as a biotech region. One of the companies there is Milenia Biotec, which was set up in 2000 in Bad Nauheim and is now based in Giessen.***

Milenia Biotec develops biomarker tests which offer physicians concrete and rapid decision aids for further treatment during operations. Research at Milenia Biotec is fired by the aim of making simple and readily manageable tests available for determining patient types. Tests of this kind are needed for on the spot decisions – for example in the operating theatre. Milenia's tests are in fact so simple to handle and evaluate that they can be carried out practically everywhere. As a new field of application, the company is at present working jointly with the Charité Berlin to develop a test using non-



**Test kits are becoming ever easier to handle**

*"Close cooperation with universities makes it possible to put solutions into practice more quickly. Central Hessen also offers us a number of opportunities which we are already following up."*

**Dr. Ralf Dostatni, Managing Director of Milenia Biotec GmbH, Giessen**

Photo: Milenia Biotec GmbH

genetic biomarkers for personalised therapy in cases of bone fractures. During the operation, samples are taken at the bone split and tested for specific biomarkers. The results can be used to tell whether the person in question is one of the 15 percent of patients whose bones heal very badly when fractured, thus as a rule making a second operation necessary. If the tested parameters show that the patient is a "bad healer", drugs which stimulate ossification will be administered immediately during the first operation.

Photo: Merck KGaA

**On the search for new biomarkers**

## Reliable forecasting of therapeutic success

***In addition to diagnostic tests, a specially important role in personalised medicine is played by procedures to select patients for a particular therapy which promises to be successful.***

As a global leader for in vitro diagnostics, Abbott in Wiesbaden is also developing test systems for personalised medicine. With its "PathVysion", the company is presenting a test which makes it possible to predict whether patients are candidates for use of the cancer drug Herceptin®. Abbott is also cooperating with Pfizer on the development of a companion diagnostic test to select patients who are candidates for a novel therapy against non-microcellular lung cancer. This treatment can benefit patients with a modification of a particular gene (the ALK gene).

*"As a leading global player for in vitro diagnostics, we are also successfully developing test systems for personalised medicine. We are intensively engaged both in development work of our own and in cooperations with other large companies."*

**Hubertus Reuter, Regional Director DACH of Abbott Molecular, Wiesbaden**

Photo: Abbott

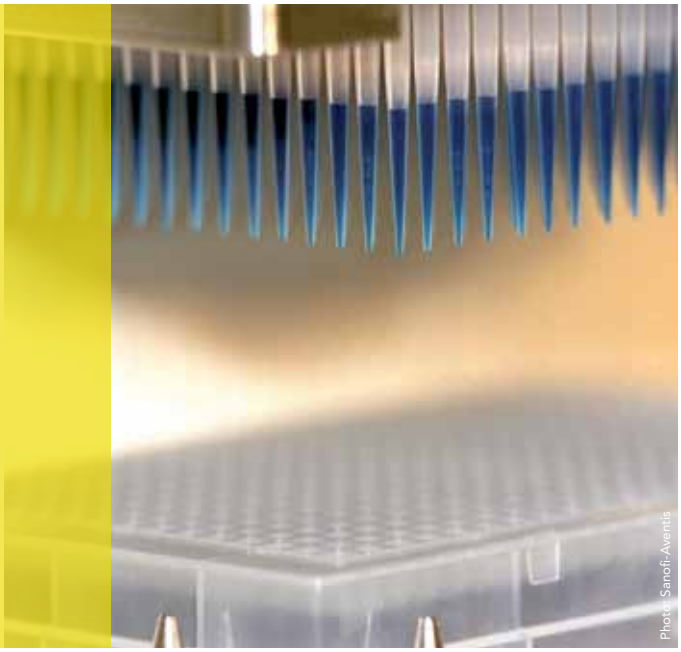


Photo: Sanofi-Aventis

Laboratory diagnostic tests help to avoid hazardous therapies

# Eliminating side-effects as far as possible

***The pursuit of a well-considered niche strategy involving the accumulation and development of highly specific know-how has turned many a medium-sized company into a global market leader.***

Immundiagnostik AG in Bensheim (South Hessen) has been pursuing this niche strategy for several years. It already supplies a number of test systems for personalised medicine and is continuously replenishing its product portfolio from a well-filled pipeline of in-house developments. In all its activities the company is deliberately on the lookout for "unoccupied niches". This strategy has transformed the company since its foundation in 1985 into an international actor in the field of diagnostics, with representations in over 30 countries. A typical example of the success of this strategy is a molecular biological test to search out genetic variations in cancer patients who react to certain chemotherapeutic agents with serious side-effects. By this means it is possible in advance to identify patients for whom the treatment is highly dangerous and thus to avoid a hazardous therapy.

Immundiagnostik AG exploits the full range of its niche. It also provides test methods which allow the personalisation of modern therapies for chronic inflammatory diseases of the intestine such as Morbus Crohn. These inflammatory diseases are steered by the transmitter TNF-alpha, the activity of which is restricted by administration of so-called TNF-alpha blockers. The test system, which recently came onto the market, shows the level of TNF-alpha blockers – a low level gives an early indication of problems the patient may have with tolerance or metabolisation of the drug. With this method the therapy of IBD patients can be much better controlled and adverse reactions avoided.

However, the company has yet more expectations for the future. Not only gastroenterologists prescribe TNF-alpha blockers but also rheumatologists. They too could profit from the opportunity to monitor drug levels.

Photo: Immundiagnostik AG

***"We are today developing tests for basic and applied research which tomorrow will help to predict and prevent diseases. Identification of disease risks, accurate forecasting, adoption of preventive measures and continuous follow-up – this is where the future lies."***

**Dr. Franz Paul Armbruster, CEO of Immundiagnostik AG, Bensheim**

# DNA tests for the right drug

***Whether a drug will be effective or whether there are likely to be burdensome side-effects can be shown by DNA tests.***

In these tests the genes which have an influence on important metabolic processes are read off and analysed for "wrong letters" in the DNA which point to mutations and misdirected processes in the human body. DNA tests of this kind are produced by Humatrix AG in Frankfurt. The company, which was set up ten years ago, was well known originally for its paternity tests, but for the last five years it has been devoting itself actively to personalised medicine. For example, it is now supplying gene analyses which can be used to determine which drugs could be potentially effective in cases of mental illness. This would eliminate the necessity to try out one psychopharmaceutical after another, thus sparing so many patients months of unnecessary suffering.

In the near future Humatrix will be launching a DNA test to establish the safety of therapy with tamoxifen. This drug is used in breast cancer therapy, and since it is a "prodrug" it must first be converted by the body to its active form. As a result of genetic variations, the enzyme necessary for this is modified in one out of every two women, which means that its activity varies.

Photo: humatrix AG

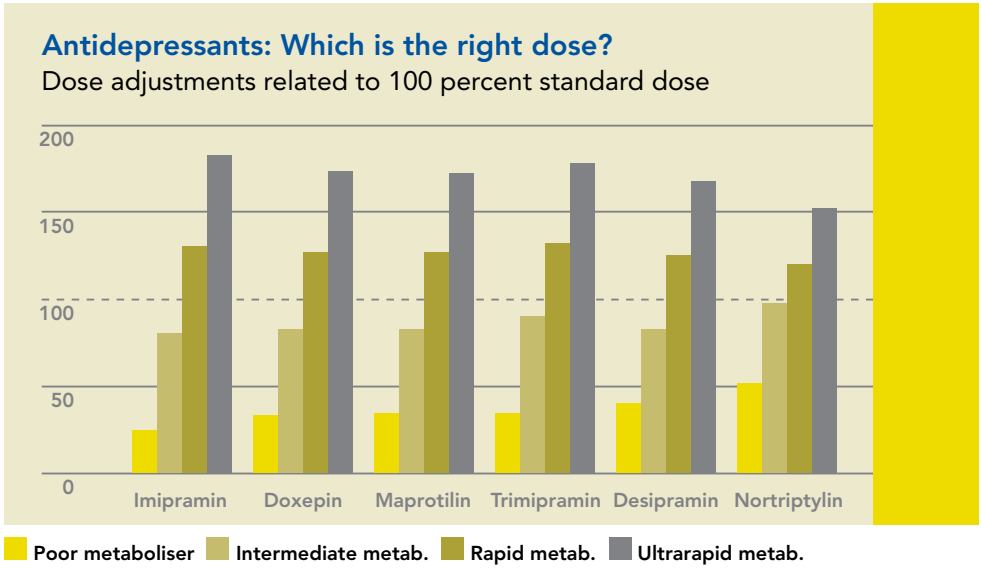
***"We urgently need clinical studies which show that a patient who receives individualised therapy because of gene typing has a better clinical result than a patient who does not receive individualised therapy. This evidence is important also if the costs are to be borne by the statutory health insurance funds."***

**Dr. Anna Eichhorn, CEO of humatrix AG, Frankfurt am Main**

If the activity of the enzyme is greatly reduced, not enough of the drug will be converted to the active form and alternative therapies should be used for the patients in question.

In addition to tests designed for patients, Humatrix is increasingly performing genetic analyses for pharmaceutical companies. These tests, which are carried out within the framework of clinical studies, aim to identify genetic variations which influence the efficacy of drugs and the duration of efficacy. The objective of these studies is to be able in future to give each patient the most efficacious drug in the optimum dose.

**Depending on whether a patient metabolises drugs slowly or rapidly, one and the same drug must be administered in different doses if it is to be efficacious and well tolerated.**




Source: Johann Wolfgang Goethe University, Frankfurt am Main

# Putting available knowledge to use

***Compiling genetic information of relevance for health is one thing, making it accessible for everyone is another. To make the information available to the persons directly affected, the Frankfurt biotech firm bio.logis is working jointly with IBM on a web portal for private customers.***

For some time now it has become evident that most of the work involved by personalised medicine is no longer genetic analysis – this is becoming less and less. The greatest challenge will be to interpret the information obtained and put it to clinical use. For this reason one of the motives behind the foundation of bio.logis in 2009 was to put the available human genetic knowledge to use as a basis for personal health decisions, since, without the help of IT systems, not even experienced human geneticists can secure an overall view of the many gene variants and their clinical consequences.

Customers can call on bio.logis to draw up their personal genetic profile. This will then be stored in a protected database to which the customer alone has access. When specific questions arise, e.g. as to the tolerability of a drug, customers can call up their genetic data and the important facts related to them. Their physicians can then also receive corresponding findings reports and use them for important therapeutic decisions.

**Correct interpretation and clinical use of information**

Bio.logis is working on the development of two major elements of personalised medicine – firstly on the further development of genetic analyses as a basis for identifying disease risks and predicting the efficacy and tolerability of drugs, and secondly on the development of new IT instruments and systems for making available the important information contained in the genes. The company, which describes itself as a "genetics information company", is thus contributing to two completely different aspects of the further development of personalised medicine.

***"What we at bio.logis call personalised medicine is a more refined subgrouping, a stratification based on individual genetic variants. In this way this will serve to make drug therapies safer and more effective."***

**Prof. Daniela Steinberger, CEO of bio.logis GmbH, Frankfurt am Main**

Photo: Dieter Schwer

# Biomarkers in drug development

## On the way to the blockbuster

***Biomarkers are highly important not only in clinical use, or in diagnostics and the identification of genetic predispositions for diseases. They are also playing an increasing part in drug development, since they enable the discovery of suitable targets for new drugs.***

One of the pioneers in drug development of this kind is Merck in Darmstadt. The company has made the search for biomarkers and stratified patient groups its general corporate strategy and up to the present time has integrated biomarker programmes in 80 percent of its entire drug portfolio. In oncology the implementation rate has already reached 100 percent – all development programmes are based on stratified medicine. In addition to oncology, Merck has also set up the functional unit "Biomarker Strategy" in all other sections such as neural diseases, inflammatory diseases and even fertility. This unit is assigned to "clinical development" with a view to integrating biomarkers as early as possible during the course of their development.

That this strategy works is shown by the monoclonal antibody Erbitux® (cetuximab), a drug which has been approved for the treatment both of metastasising colorectal cancer and of certain head and neck tumours. The antibody blocks a binding site on the cancer cell known as the EGF receptor – a therapy from which many tumour patients benefit, but not all. This makes it necessary to carry out a genetic test before the drug can be administered. The test is used to identify changes in the so-called KRAS gene, which are present in about 40 percent of the patients. The 60 percent who show no mutations will in all probability benefit from Erbitux®. Merck is confident that the drug will achieve blockbuster status by 2012.

Photo: Merck KGaA

***"Merck has long since prepared itself for stratified medicine. The search for biomarkers is integrated into most of the new development programmes for new drugs, and in oncology to as much as 100 percent."***

**Prof. Ilhan Celik, Head of Biomarker Strategy Oncology, Merck Serono, Darmstadt**

In cooperation with Oncothyreon Inc. in Seattle, Merck is performing two phase III trials for cancer immunotherapy with Stimuvax in connection with lung cancer. The drug activates the immune system against cancer cells producing a receptor known as MUC-1. This receptor is frequently observed in many types of cancer, including lung, breast and prostate cancer. Another active ingredient undergoing a phase-III trial and hence at a very advanced stage of development is Cilengitide. It is being tested in patients with recently diagnosed glioblastoma, the most aggressive form of brain tumour.

Photo: Merck KGaA

**Production and filling of Erbitux®**

# Diabetes – finding the key

***The global diabetes business of Sanofi-Aventis has been controlled from Frankfurt am Main since the beginning of 2010. The company's large R&D unit "Diabetes Division" conducts intensive research into new personalised approaches. Sanofi-Aventis is engaged here in a field where biomarker-oriented personalised medicine is not yet by any means routine practice.***

The Sanofi-Aventis team is engaged in the search for biomarkers which allow disease courses to be better predicted than at present and at the same time in the development of new active ingredients. The research group was reorganised last year in Frankfurt and since then has been constantly intensifying its activities in this area. These activities are closely tied up with other R&D functions such as biomarker imaging.

Work is being centred round type 2 diabetes, known earlier as adult onset diabetes, but nowadays ever more frequently affecting young people also. To fight the disease, the company is following two strategies. To assess more accurately which of the available active ingredient classes will be of greatest benefit to individual diabetes patients, suitable biomarkers will have to be identified. The same applies to the development of new and more efficient active ingredients. Here again, biomarkers play a decisive role. In Frankfurt, both of these aspects are being pursued in parallel. For this purpose large numbers of patient data will be needed.

Photo: Sanofi-Aventis

**Genetically engineered insulin production**

Since many of the research issues are in the precompetitive area, there are opportunities here for cooperations. The company is consortial leader for several projects at the same time. One of these is "imidia", a network in the "Innovative Medicines Initiative" (IMI) in which experts from various institutes, research organisations and biotech companies focus on the development of novel biomarkers and on the organisation and function of insulin-producing cells.

## New combinations against cancer

In December last year, Sanofi-Aventis announced the start of a global research and development cooperation between Sanofi-Aventis U.S. Inc. and Merck KGaA in Darmstadt. The two companies plan to carry out joint research into novel experimental active ingredient combinations against cancer which could block specific signal pathways in the malignantly transformed cells. Tumour cells frequently "rescue" themselves when one of their signal pathways is cut off by using other pathways. But if several of these central pathways in the cell are blocked at the same time, it might prove possible to treat tumour cells more effectively than at present. The companies are already planning to try out combinations of their active ingredients in phase I trials in the near future.

Photo: Sanofi-Aventis

***"We are working on a specially tailored biomarker programme to identify and improve the efficacy and potential uses of our active ingredients."***

**Dr. Mark Brönstrup. Research & Development/ Diabetes Division, Sanofi-Aventis Deutschland GmbH, Frankfurt am Main**

### CI3 – Network for the medicine of the future

Influencing of the immune system as a means of treating serious diseases has great potential in individualised medicine. Immunotherapeutics possess very high specificity and affinity for their target. They are used for patients who actually carry the target, which means that antigen-specific immune interventions can become a promising therapeutical approach. However, new cooperative solutions in research, development, production and distribution will be necessary if the complex immune system is to be of real clinical use in the struggle against diseases. To this end, the Cluster for Individualised Immune Intervention (CI3) brings together key companies, research facilities and other health business actors not only in Hessen but also in Rhineland-Palatinate, with the aim of making the Rhine-Main region an international leader for individualised immunotherapeutical drugs and treatment approaches. For this purpose, CI3 in Mainz has created a network of actors from economy, research, health care and politics, thus serving as the integrative element along the entire innovation and value chain. Project partners in Hessen include the Technical University in Darmstadt, the Goethe University in Frankfurt, the Paul Ehrlich Institute in Langen, the Georg Speyer House, Abbott, Biotest, Sanofi-Aventis and Merck.

# Clinical studies for personalised medicine

***To obtain evidence that new drugs are effective and well tolerated in practice, they must be tested in clinical studies.***

Since personalised medicine focuses deliberately on treatments for subgroups of particular diseases, it is often difficult to find sufficient numbers of participants for clinical trials. For this reason, international cooperations have become standard practice. But solutions are also being sought within Germany itself. One example here is a regional Translational Cancer Consortium built up by Professor Hubert Serve at the University Centre for Tumour Diseases (UCT) in Frankfurt am Main. The university clinics in Frankfurt am Main and Mainz, together with eight other hospitals in Hessen, are taking part in it with a view to improving the study situation for solid tumours. Serve hopes that his Hessian initiative will have a signal effect throughout Germany as a whole, particularly since the model project has been chosen by the Federal Ministry of Research as one of the partners for the National Consortium for Translational Cancer Research.

Under the lead responsibility of Professor Helmut Schäfer from the Institute of Medical Biometry and Epidemiology in Marburg, a joint project is being carried out together with the universities of Giessen and Frankfurt am Main to develop new designs for clinical studies in personalised medicine. One of the aims of the proposed research project ADAMED (adaptive statistical methods for individualised medicine) is to achieve a flexible adaptability to the data which will enable the knowledge obtained to be focussed during the course of the study to a particularly promising subgroup. ADAMED could make phase II trials unnecessary and permit a reduction of the numbers of patients needed.

Photo: UCT, Frankfurt am Main

***"Cancer diseases are not due to a single mutation but to a combination of many mutations. At the same time new drugs will constantly become available to neutralise the results of single mutations. The decisive thing will be to combine the new drugs correctly for each individual patient."***

**Prof. Dr. Hubert Serve, Scientific Director of UCT, Frankfurt am Main**

# Finding the Way into Practice

***Future studies clearly indicate that personalised medicine is an important trend, possibly even a megatrend. It is expected that personalised medicine will decisively shape the health system in the years to come. However, the way leading from research to practice will involve numerous changes for all concerned, especially for patients and physicians.***

Modern patients are considered to be informed patients who are informed about their diseases and the possible methods of treatment. It is with this awareness that they go to consult their physician, and they expect to have a say of their own with regard to therapeutic options instead of simply having a particular therapy prescribed. Personalised medicine goes a step further by giving patients for the first time the chance to receive information on their personal genetic profile, on the basis of which deductions can be made about health risks or already existing diseases. In this way they come to understand the reasons for a particular treatment, which in turn enables them to assume responsibility for their own health and, in cases of doubt, to adapt their lifestyle to match their individual risks. Personalised medicine will thus have significant effects on public health.

The basic approaches of personalised medicine make the advisory role of physicians more important – interpretation of genetic data calls for expert knowledge. However, this presupposes solid knowledge of genetics and pharmacology on the part of the physicians, but these are areas where medical training is not as yet offering sufficient preparation. Hence it is not unlikely in future that practitioners working directly with patients will be joined by physicians specialised in analytics who will act, so to speak, as genetic advisers and provide support for practitioners and patients alike.

The advisory role of physicians will grow

## The basis is not yet broad enough

If personalised medicine is to be established in wide areas of healthcare and also to become reality for local practitioners, still more biomarkers and active ingredients will have to be found. At the present time personalised medicine is clearly focused on tumour treatment. However, the greater the number of therapeutic areas covered, the easier it will be for the concept to secure a firm footing in the clinical routine of physicians and in the awareness of patients. And only when personalised medicine has attained a critical mass will it be possible to reap the additional benefits referred to above.

With its small and medium-sized biotech firms, together with the global players in the pharmaceutical sector, Hessen is in an excellent position to press ahead with this approach. A great deal of work is going on in Hessen, which has a rich tradition in medicine and pharmaceutics. But research and development are not everything. Nowadays more than ever the social acceptance factor must also be taken into account. The main source of distrust in personalised medicine is concerned with data protection. To attain broad public acceptance, the data protection questions associated with the storage, transmission and use of genetic data will have to be cleared. This is all the more necessary since personalised medicine is another area where not only physicians and patients but also various other parties are involved in the diagnostic and therapeutic system and thus come into contact with sensitive genetic data. However, Hessen is among other things one of the leading IT regions, and for this reason it is not surprising that answers to these questions are already being developed here.

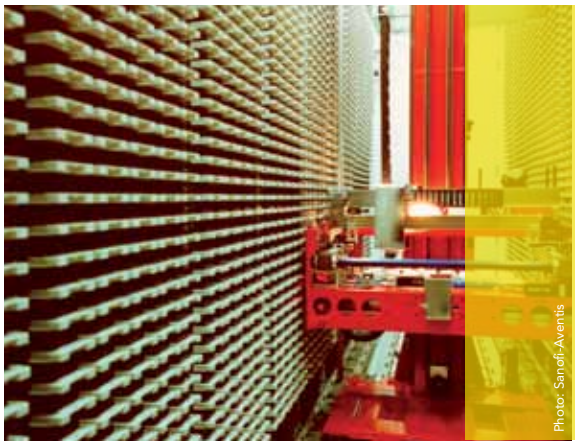


Photo: Sanofi-Aventis

**Closer networking of biobanks**

## Networking needs standards

Customised therapies cannot be developed successfully without so-called biobanks (biomaterial banks) where body substances such as cells, tissues and blood are collected, together with the clinical data of the patients. The purpose of the National Biobank Register currently being built up is to make the multiplicity of smaller and larger German biobanks available at national and international level and to network them with the aim of advancing German high-level research into the molecular causes of diseases. As is the case with all allocated resources put to decentralised use, standardisation, codification and quality assurance are a sine qua non. The introduction of uniform quality standards is thus also indispensable in the field of biobanks. Nowadays every university clinic has its own biobank and its own procedures for freezing, storing and dispatching samples. Moreover, there are no standards, national or international, for the questioning of patients during the collection of clinical data or for the periods of time during which these data are stored. With the new platform it is planned to alter this. The platform can be used by scientists to exchange information, experience and samples, and also, not least of all, to initiate research cooperations. The National Biobank Register will therefore constitute a decisive milestone in the development of personalised medicine.


**The security engineering group at Darmstadt Technical University**

### Hessen also a pioneer in data protection

Scientists at the CASED Security Centre and Darmstadt Technical University have presented solutions for this problem. Professors Stefan Katzenbeisser and Kay Hamacher have developed a mathematical method which allows simultaneous use and protection of encoded genomic data.

Hessen is also well to the fore with regard to data protection regulations in biobanks. Up to now the only seal of quality for biobanks comes from an independent data protection centre in Schleswig-Holstein. Hessen's data protection officer, Professor Michael Ronellenfitsch, is aiming to change this. His objective for 2011 is to have evaluations of this kind issued by the highest regional authority. Attestations of security should thus no longer be a matter for a private organisation but for a sovereign public authority, thus assuring greater credibility. The data protection officer sees Hessen in a role model function as regards data protection in the healthcare field and wishes to take on this function in the interest of the citizens.

## The Outlook

***Modern metrological methods are making biomarkers visible step by step, like separate pieces of a jigsaw puzzle. More and more of the pieces are being discovered. The work is driven principally by small and medium-sized companies with highly specialised activities.***

In a few years from now these pieces of the puzzle will have been put together to form an overall picture, and we will be able understand complex disease processes at the molecular level. Medicine will then really enter a new era and take a quantum leap forward. This extensive body of knowledge, which opens up for us the congruence of molecular and biological processes, will allow us to make widespread use of personalised medicine, with all the benefits this brings not only for therapy but also for the national economy. It will revolutionise medical checks, diagnosis and therapy. The misdirection of financial resources, which due to insufficient awareness of complex interactions is at present a normal part of our healthcare system, could be greatly reduced. And, most important of all – we will be able to provide better help for sick persons.

As a region with many innovative and highly competitive biotech companies along the value chain of stratified medicine, Hessen is now already in an excellent position – with research into, and development of, new biomarkers and active ingredients, the provision of suitable conditions for efficient studies, and the identification of solutions for social issues. This confirms Hessen's economic policy, and at the same time places it under an obligation for the future.

## Imprint

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