



Roadmap

*for the German Health Research Program
of the Federal Government*

Executive summary

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Core working group introductory remarks

In November 2004 following detailed discussion the Health Research Council (GFR) of the Federal Ministry of Education and Research (BMBF) decided to draw up a Roadmap ahead of the design of the Federal Government's new Health Research Program. Its purpose is to provide guidance on addressing major health research issues in future.

The issues regarded as important are those which

- are expected to produce real advances in medical research if specific support with additional resources is given
- will lead to improvements in diagnostics, therapy, prevention or rehabilitation in important medical fields
- will provide stimulus for the development of new products and therefore trigger opportunities for economic growth.

The kinds of issues that should be identified are those in which specific funding can enable Germany to occupy an outstanding position in the international arena or to improve its already very good position even further.

To plan and supervise drafting of the Roadmap the Health Research Council has appointed a core working group consisting of four members from its own ranks.

To us as members of the core working group it became very clear that a Roadmap of this kind can only produce consistent findings and achieve acceptance if it is based on broad

expert knowledge. For this reason, the process of drawing up the Roadmap was based on a written survey of just under 900 respondents and a subsequent evaluation of the issues raised by six working groups comprising 110 representatives of science and industry altogether.¹ While the written survey focused on identifying and substantiating major research issues, the working groups' task was to subject the proposed topics to critical evaluation regarding their innovative contribution to research, to medical care and to opportunities for economic development. The working groups were also asked to assess the chances of research topics being successfully implemented in Germany and to prioritise them with respect to all aspects mentioned before.

In planning the methodology we assumed that crafting the Roadmap could only be performed by organisation into working groups to allow lively discussions. In each working group scientists specialised in various subjects were invited to participate: scientists specialised in basic research, clinical scientists and those specialised in health services research and epidemiology. In addition, industry representatives were also included.

¹ Working group members are listed in the long version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf).

Working groups were established for the following six major disease areas:

- Musculoskeletal disorders
- Nutritional and metabolic diseases plus endocrinological diseases
- Cardiovascular, lung, kidney diseases
- Infections, chronic inflammation and inflammatory skin diseases
- Cancers
- Neurological and mental illnesses plus diseases of the sense organs

Reasons for organisation of working groups according to these six disease areas were the following: the Federal Government's Health Research Program is essentially targeted towards clinical research. It is therefore obvious to put the main emphasis on topics of clinical relevance and especially on such diseases, which impose the most significant burden of disease to society.

Apart from providing an initial framework for the Health Research Program and focussing on the areas with most important burden of disease there was another point, which influenced our decision to organise the drafting of the Roadmap along different medical fields: there is a marked gap between basic research and clinical research. Fresh insights from basic research find their way into clinical research too slowly and not substantially enough. They are not evaluated properly as to whether they might help diseases to be better understood, diagnosed earlier, prevented before onset and even to be cured. With better knowledge of the problems of

clinical care, some detours in basic research could be avoided and the design of some research projects could be more targeted from the beginning. Translating basic research results via clinical research into applications is a special challenge for an effective and efficient health research policy.

Even though many experts have helped to draft the Roadmap, this is no proof that its correctness is beyond doubt. Despite all the care taken in drafting it, it is impossible to rule out that issues may be prioritised and weighted differently from another perspective and that important new issues will emerge, whose significance cannot be properly recognized today. The half-life of such forecasts should not be set too high as well. It will never be possible either to avoid that an assessment of the importance of issues is dependent on the viewpoint or vested interests of the observer. It would not meet our approval to use the Roadmap as an instrument to sort topics into "important" and "unimportant" when choosing, assessing or funding research topics. No funding organisation, research institute or scientist can be displaced of their own critical assessment and decision for the selection of topics; the Roadmap can only provide guidance, overview and suggestions.

In the Roadmap the strengths and weaknesses of health research in Germany are only specified with respect to the taking up or pursuing of research issues. For methodological reasons these assessments could additionally be substantiated via bibliometric analyses only in some cases. The Roadmap does not contain any comprehensive analysis of the structures of German health research, with the basic parameters, structures of research institutes and funding methods being critically examined. Such analyses have already been

sufficiently documented by other official statements in particular by the Science Council (WR), the German Research Foundation (DFG) and the Health Research Council (GFR).²

We are confident that the Roadmap's findings will provide help and guidance with the new version and ongoing development of the Federal Government's Health Research Program and will be intensely consulted by those responsible at the Federal Ministry of Education and Research (BMBF) on issues related to designing the program and setting up new funding priorities. We also hope the Roadmap will give orientation and helpful suggestions to other health research facilities, funding organisations, research institutes as well as medical schools when setting up their own priorities or research strategies.

We would like to thank the many individuals involved who contributed their time and effort to create the Roadmap.

Our thanks also go to the BMBF, which enabled the creation of the Roadmap in two ways: it has borne the costs of planning, implementation, documentation and publication. With the Health Research Program the BMBF has given the Roadmap process a field for application, without which the entire project and the committed collaboration of many scientists would have been impossible. It was a bold and hopefully successful and forward-looking decision of the BMBF to base the design of a specific research program essentially on a bottom-up process.

Finally, we would like to thank the project management agency (PT-DLR), which did an excellent job on behalf of the BMBF in handling all the logistics, documentation and analyses required.

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² References:

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- *Workshop documentation: Hochschulmedizin der Zukunft: Ziele und Visionen für die klinische Spitzenforschung, joint workshop of the BMBF, DFG and Science Council in Berlin on 10/11.05.2004 (http://www.gesundheitsforschung-bmbf.de/_media/Hochschulmedizin_der_Zukunft.pdf)*
- *Workshop core demands: Hochschulmedizin der Zukunft: Ziele und Visionen für die klinische Spitzenforschung on 10/11.05.2004 (http://www.gesundheitsforschung-bmbf.de/_media/Hochschulmedizin_der_Zukunft_Kernforderungen.pdf)*
- *Förderung des Wissenschaftlichen Nachwuchses für die Hochschulmedizin; position paper of the working group promoting young researchers of the BMBF Scientific Committee of the Health Research Council on 08.03.2004 (<http://www.pt-dlr.de/pt/gf/GFR/Nachwuchs.pdf>)*

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1. Summary

The Roadmap for the Federal Government's Health Research Program was based on the question of what are likely to be the major research issues in health research that can be dealt with successfully in Germany in the next few years. Regarding the new version of the Health Research Program, the Health Research Council (GFR) had recommended a planning process of this kind to the Federal Ministry of Education and Research (BMBF) in November 2004. The issues considered important were those which

- are expected to produce significant advances in expertise,
- will lead to either direct or indirect improvements in diagnostics, therapy or prevention of major medical problems,
- will provide impetus for the development of new products or services.

The issues to be identified in particular are those, which can be dealt with in approximately five to ten years and where definite advances can be expected in at least one of these dimensions and in which Germany can achieve an outstanding position in the international arena or improve on its good position even further with targeted funding.

Effective and high quality medical care requires efficient health research. Without health research there are no medical advances in curing diseases – of which many today are still incurable – and in relieving medical suffering. Without health research the advanced level of health care already achieved cannot be maintained. The task here is to undertake research in Germany at an internationally competitive level and deploy

resources as effectively as possible. With the Roadmap process an analysis was done into what contribution Germany can make to the three goals specified above, how research is set up in Germany, where its strengths lie domestically and where potential or gaps in health research exist, so that Germany can make a substantial contribution within the EU and internationally. The result is specific to Germany.

At around the same time or shortly before, other countries have conducted initiatives for research foresight and planning, e.g.

- the European Strategy Forum for Research Infrastructure (ESFRI), which published its report on the “Roadmap for European Research Infrastructure” in 2006;
- the French Ministry for Business, Finance and Industry, which presented its “Technologies clés 2010” study in 2006;
- the British Office of Science and Innovation, which reports to the Science Advisor to the British government and began a Foresight Program over several years in 2002;
- the National Institutes of Health in the USA, whose Roadmap started in 2002.

The above-mentioned international initiatives vary in the breadth of their scope. The Health Research Council's idea to set up a national specialist program in its entirety via a foresight process is unique.

If we compare the issues mentioned resulting from these initiatives with those of the Roadmap process for Germany's Health

Research Program, similar trends and requirements are discernible internationally. These include translational research, nutritional research, innovative imaging, biobanks, animal models, vaccine research and brain research.

The concept of conducting the Roadmap for the Health Research Program was put together by four scientists appointed by the GFR from its ranks (referred to below as the “core group”) with support from BMBF’s Health Research Department and the PT-DLR project management team commissioned by the BMBF.

It was this core group’s task to attend to and manage the entire process. It was implemented by forming working groups to address six of the most serious medical problems in terms of morbidity and mortality – the minor subjects were included as far as possible with the major issues, as there are many cross-references:

- Musculoskeletal disorders
- Nutritional and metabolic diseases and endocrinological diseases
- Cardiovascular, lung and kidney diseases
- Infections, chronic inflammation and inflammatory skin diseases
- Cancers
- Neurological and mental illnesses and diseases of the sense organs

These working groups comprised a total of 110 scientists with various research interests (e.g. basic research, clinical research, preventative research, operative/conservative types, health service research, epidemiology). When selecting them, their professional breadth and multidisciplinary perspectives

were the main factors. To identify the research issues, initially a written survey was conducted online among just under 900 scientists from universities, extra-university research facilities and industry in Germany. (The mean response rate for the six working groups was 36 percent). As well as being identified, all the proposed topics were subjected in the working groups to a critical examination in terms of their innovative contribution to the research, the health service and economic development opportunities in an international comparison as well. In addition, the working groups assessed the chances of implementing these research topics in Germany and established a prioritisation of issues (by peer-review). Apart from being assessed by the scientists the data available on financial resources from third party funding and institutional extra-university research in Germany between 2000 and 2005 and some bibliometric analyses were added.

When selecting the research issues both single discipline as well as multidisciplinary or method-oriented multidisciplinary issues were identified. The working groups proposed and elaborated on a total of 74 research issues, including 16 multidisciplinary issues.

The research issues prioritised by the individual working groups (Table 1) and multidisciplinary issues (Table 2) are listed below. How the issues were dealt with is presented in detail in the full version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf). The following sections related to individual medical conditions (2.1.–2.6.) are a summary of the issues proposed. The multidisciplinary issues proposed by the various working groups are summarised in an overview in section 2.7.

Table 1: Prioritised research issues

Working groups and respective research issues	page
Musculoskeletal disorders	
Molecular mechanisms of inflammation and regeneration	12
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Nutritive and hormonal regulation of food intake: the brain as a target of anti-adipose and anti-diabetic therapy	14
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Bio-hybrid organs – organ replacement and tissue engineering	17
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Molecular diagnostics: imaging and biomarkers	17
Therapeutically applicable molecular target structures: identification and preclinical validation	18
Remodelling including organ fibrosis and reverse remodelling with chronic diseases	18
Sub-clinical dysfunction of heart, lung, kidney and metabolic system – risk potentiation due to interactions	18

Infections, chronic inflammation and inflammatory skin diseases	
Targets for anti-infective therapies	20
Identification of immunoeffector programs to improve immunoprophylaxis and therapy	20
Genetic determinants of susceptibility to infectious diseases	20
Medical suffering due to infections and the efficacy of population-related interventions – epidemiological study proposals and cross-linking of data	20
Development of new animal models	20
Cancers	
Migration, invasion, metastasis, tumour stem cells, dormancy	22
Therapy resistance, sensitivity	22
Tumour host relationship, microenvironment, age, senescence	23
Immunotherapy, gene therapy and tumour vaccination	23
Prolonged survival and consequences of therapy	23
Clinical genomics: implementation of diagnostic methods in studies; predictive and prognostic genetic and transcriptional patterns (signatures)	23
Innovative imaging	23
Neurological and mental illnesses and diseases of the sense organs	
Physiology and pathology of synaptic processes	25
Neurobiology and psychobiology of aggressive, impulsive and addictive behaviour	25
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Neurosensomics	26
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Table 2: Multidisciplinary issues

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Medical suffering (e.g. due to infections) and efficacy of population-related interventions – epidemiological study proposals and cross-linking of data	
Innovative imaging	
Molecular diagnostics: imaging and biomarkers	
Clinical genomics: implementation of diagnostic methods in studies; predictive and prognostic genetic and transcriptional patterns (signatures)	
Multi-organic translational research	29
Therapeutically applicable molecular target structures	
Development of suitable new animal models	
Inflammation related organ fibrosis	
Remodelling including organ fibrosis and reverse remodelling with chronic diseases	
Organ regeneration due to stem cells	
Cell ageing	
Customised medicine	
Health service research	29
Research to implement current knowledge on chronic diseases in routine care	
Research to transfer scientific findings into clinical practice	
Evaluation of multi-modal therapeutic concepts	
Palliative medicine	

2. Selected research topics

2.1. Musculoskeletal disorders

Musculoskeletal disorders caused by disease or injuries have a huge impact on society and impose an enormous economic burden worldwide. Apart from maintaining cognitive abilities and the health of the cardiovascular and metabolic organs, maintaining physical fitness and mobility into old age is one of the great medical challenges today. In Germany one third of patients who sees a GP suffers from musculoskeletal disorders. One in six hospital treatments and one in three inpatient operations are due to disorders of the musculoskeletal system. In 2002 musculoskeletal diseases and injuries were the cause of 40% of all sick days off work, of 42% of all rehabilitation services and of 25% of all early retirements. Altogether, these disorders account for 16% of health spending and are the biggest cost factor in the German health care system. Considered in terms of lost production, the estimated total cost of musculoskeletal disorders is more than €100 billion a year or 4.8% of GNP.

Acute and chronic back pain, osteoarthritis, osteoporosis and inflammatory rheumatic diseases are the major musculoskeletal diseases. Based on their frequency and their considerable severity they have a huge and increasing economic significance. These diseases cause pain and disability and thus have a high impact on the patient's quality of life and earning capacity. For back pain the lifetime prevalence is 80%. It represents the most important cause of inability to work and early retirement and accounts for a considerable portion of direct sickness costs. The causes of back pain remain unknown in

about 80% of cases. Therefore only the symptoms are usually treated, which is often rather ineffective. Joint disorders such as osteoarthritis or rheumatoid arthritis are the main cause of disabilities in industrialised countries. Sixty percent of 65-year-olds in Germany suffer from this condition and its frequency rises with increasing age. Every year 300,000 patients with osteoarthritis have an artificial joint replacement because currently there are no therapies available to target the cause of the disease. Osteoporosis affects a total of 7.8 million people in Germany. Two thirds of femoral neck fractures are due to osteoporosis.

In recent years, research into inflammatory rheumatic diseases and osteoporosis has made great progress. Combination therapy with well-known and new disease-modifying antirheumatic drugs (DMARDs) as well as biological response modifiers have greatly extended the therapeutic possibilities available for inflammatory rheumatic diseases and created new options especially for patients with severe disease. However, this treatment has to be given continuously and several patients fail to respond even to the new biological response modifiers. In future functional genome research is expected to identify molecular signatures and biomarkers which allow for a better prognosis of the disease course and of the efficacy of the different therapeutic strategies in the individual patient. With the introduction of new pharmaceuticals the treatment of osteoporosis has also significantly improved over the last ten years allowing to develop new therapeutic guidelines of high quality. Other new therapeutic principles are presently in preclinical and clinical stages of pharmaceutical develop-

ment. However, the new therapeutic and diagnostic possibilities available have still hardly made their way into guideline-directed medical practice, leading to a severe undersupply to the patients. Although research into the biology of articular cartilage has already made great progress, up to now it was impossible to develop drugs which inhibit the degenerative structural changes of cartilage responsible for disease progression or even bring about reconstruction of damaged cartilage. The reason for this is the complexity of the pathophysiological process. Among the significant factors in the pathogenesis of osteoarthritis are changes in the subchondral bone, inflammatory processes and mechanical overloading of the affected joint. Considerable efforts have already been undertaken to clarify the significance of these various pathogenetic routes. Recently new therapeutic approaches to restore damaged articular cartilage based on tissue engineering of autologous chondrocytes raised considerable interest.

Further ageing of the population in industrial countries will lead to a further increase in patient numbers suffering from musculoskeletal disorders. Therefore, measures are urgently needed to ensure a rapid translation of research findings into clinical practice, to implement preventive measures and optimise health care provision. To this end the World Health Organisation (WHO) and the United Nations (UN) have declared the years 2000 – 2010 as the “Bone and Joint Decade”. In North America as well as on European level (e.g. in the 7th framework program), musculoskeletal disorders and injuries are represented for the first time as major diseases with high research priority.

With regard to these considerations the working group on musculoskeletal disorders has prioritised a number of research topics, which are briefly presented in the following. A more

detailed description of all the recommended research tasks is included in the full version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf).

Molecular mechanisms of inflammation and regeneration

This is a highly significant research topic. Research findings in this field will have a substantial impact on health care and pharmaceutical research and development. One example is the introduction of TNF α -Blockers and other “biologics”. Within German research on musculoskeletal disorders this field represents the most widely developed one. There are plenty of outstanding and internationally competitive scientific working groups, which make highly efficient use of the available research structures. This research field should also be supported in future in order to maintain and expand on Germany’s favourable position.

Stem cells and molecular signalling pathways in the development, maintenance and regeneration of mesenchymal tissue

This research field is of key importance for developing innovative treatments and holds great promise for the future. It is a highly significant research topic but will only have an impact on health care in the long run. Up to now Germany yields no internationally leading groups in the field of mesenchymal stem cells. However, in recent years several research projects have been set up that may lead to the establishment of powerful groups. A close cooperation between the recently established Centres for Regenerative Therapies and the very well developed German research in developmental biology and cell differentiation can result in further considerable progress.

Translational research on fracture healing, bone defects and osteoporosis

A thorough understanding of the mechanisms leading to the regeneration of functional bone tissue is mandatory for developing approaches to support and enhance the natural occurring healing and regeneration processes if necessary. German research in fracture healing and osteoporosis differs considerably regarding their extent and quality. In fracture healing Germany is an international leader. German osteoporosis research has also made substantial progress during the last 15 years. However, it still suffers from structural problems and is well established at only a few university hospitals. To cope with the upcoming research tasks, successful interaction between the two research fields has to be developed and representation of these issues at the universities has to be promoted.

Evaluation of complex therapeutic strategies for musculoskeletal disorders in routine medical care

Hitherto, the complex therapeutic approaches usually applied for the treatment of musculoskeletal diseases have barely been evaluated under the conditions of routine medical care. Therefore the proposed research topic is of huge importance, especially for the improvement of patient care. Research findings acquired from this field, form the basis of new evidence-based guidelines and the effective use of resources in the health care system. Previously, evaluation of therapeutic procedures has largely been determined by industrial interests (e.g. phase IV studies for new drugs). Public authorities have not been much involved. Future research projects should concentrate on a few but extensive studies, which should be preceded by pilot studies to examine feasibility. To perform such studies it is also important to involve partners from a variety of different disciplines.

Other major topics

The working group has also chosen further major research topics in the field of musculoskeletal diseases. These include identification of genetic and environmental factors, which play a role in the development and onset of osteoporosis and osteoarthritis. Diagnosis and therapy of osteoarthritis have to be improved. This also applies to disc related back pain. The development of experimental animal models may strongly facilitate research in these fields. Research should also be carried out in future on the molecular mechanisms of the cellular ageing of mesenchymal tissue, which plays a part in degenerative diseases of the musculoskeletal system, as well as on the molecular basis of interactions between kidney and bones. In addition, the development of innovative therapies for diseases of the musculoskeletal tissue is urgently needed. In this respect the investigation of regenerative and tissue engineering approaches holds great promise. Another major object of research should be the implementation of evidence-based knowledge in routine health care. Because of its relevance to all chronic diseases this cross-sectional issue is of enormous significance for health care provision in general.

General recommendations

Compared with the significance of musculoskeletal disorders in health care the respective German research is still not sufficiently developed. One reason is that so far only limited resources have been invested into clinical research in orthopaedics and trauma surgery. Due to missing prospects for career there is a shortage of both research and clinical scientists. To improve this situation more research professorships should be appointed at orthopaedic and trauma surgery departments of university hospitals. Furthermore, a variety of promising research approaches should be supported to reveal their potential and integration of basic and clinical research should be strengthened via networking programs.

2.2. Nutritional and metabolic diseases plus endocrinological diseases

Nutrition, metabolism and endocrine control are closely connected processes. The control of homeostasis and the adaptability of the metabolism reduce external nutritional influences and prevent imbalances. Regulation of the metabolism evolved in an environment in which both energy from food as well as a qualitative supply of nutrients was always limited and high-energy consumption was part of everyday survival. However, today these regulatory mechanisms often cause problems. Modern lifestyles and eating habits involving energy-rich food and lack of exercise at the same time favour overweight and obesity, which are the primary patho-physiological factor in the development of most lifestyle-related diseases. Overweight and obesity thus give rise to cardiovascular diseases, diabetes type 2 (DMT2) and various types of tumour. These problems affect all advanced societies and are on the increase. In the next ten years a further increase in type 2 diabetes alone of around 25% is expected in Europe. In Germany the prevalence of overweight rose from 8.9% in 1994 to 15.7% in 1999 and obesity from 10.1% to 13.1% in the period 1994 to 1998. It is particularly remarkable that obesity and DMT2 frequently occur together among children and adolescents. The prevalence of DMT2 in Germany among children and adolescents is approximately one percent. The average costs of medical treatment for an obese child in the 5-20 age group in Germany in 2003 were €3,500 and approximately €8,500 per treated obese child with diabetes type 2.

Apart from obesity, diabetes and tumours, musculoskeletal disorders, various chronic inflammatory processes and dementia are also associated with lifelong high calorie food

intake. Therefore, the issues to do with nutrition, metabolism and endocrinology are an interdisciplinary topic that spills over into various medical conditions and research fields. The major task of this research field is to characterise the body's functional interaction with nutrition in order to clarify the connection between nutrition and the onset of disease and in turn develop the appropriate strategies for prevention and therapy. As early as 2001 the BMBF's FUTUR process also identified prevention as one of the four visions of research policy in Germany. The vision statement "Healthy and fit to a ripe old age" described a society in which each individual achieves this goal through health-conscious behaviour and action and creates the motivation for it via a "health-promoting lifestyle". The task of research and development is to create the conditions for effective prevention in the future.

Against this background the working group on nutritional and metabolic diseases and endocrinological disorders classified a number of research topics as having priority, which are presented briefly here. A detailed presentation of all recommended research tasks is included in the full version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf).

Nutritive and hormonal regulation of food intake: the brain as a target of anti-adipose and anti-diabetic therapy

The energy homeostasis of the body is determined and regulated via several partly overlapping sensory systems. The brain includes all the information on the nutritional situation and directs a coordinated response via neuronal or humoral signals to the target organs. Dysfunction of these mechanisms change the homeostatic control functions of the CNS and favour the onset of disorders such as obesity and DMT2. A better understanding of these neuronal control circuits and

their signal molecules will be encouraged by investigating new central, gastrointestinal and peripheral therapeutic options to control obesity and DMT2. Research findings on this subject are also highly significant for industrial use.

Molecular mode of action of nutrients

Apart from energy consumption, specific nutrients and non-nutritive substances in food also have an effect on metabolic events. This is proven by the large number of nuclear receptors for nutrients. These receptors influence metabolic responses in an organ-specific manner by changing the gene expression. As such, great significance is attached to understand the mode of action of specific substances and the quality of nutrition in the same way as its energy consumption for the onset of lifestyle-related diseases.

Development, degeneration and regeneration of hormone-producing cells

Hypercaloric nutrition rich in carbohydrates and fats raises insulin level constitutively and leads to insulin resistance. With glucotoxicity and lipid toxicity processes are compounded whereby pathophysiological changes are triggered in various tissues. Hormone-producing cells (β -cells, thyroidal cells) are especially affected and as a result, they lose their functionality. New research projects to “rescue” these cells or replace them are thus very important.

Foetal and infantile focus: significance for the development of obesity, diabetes and other chronic diseases

Compliance with any nutritional medical measures is reflected in nutritional behaviour (both in malnutrition as well as super-nutrition) as well as its preventative, therapeutic and economic success. New strategies for sustained modification of lifestyle behaviour are therefore urgently required.

Nutritional behaviour: mechanisms, implementation strategies and economic consequences

Compliance with any nutritional medical measures is reflected in nutritional behaviour (both in malnutrition as well as super-nutrition) as well as its preventative, therapeutic and economic success. New strategies for sustained modification of lifestyle behaviour are therefore urgently required.

Mitochondria, energy metabolism and ageing

Oxidative processes in mitochondria are not only of particular relevance for ageing. Mitochondrial malfunctions are also closely associated today with the onset of cardiovascular diseases, DMT2, muscular and neurodegenerative disorders and tumour genesis. Thus, investigation of the nutritive and endocrinological modulation of mitochondrial functions is the focus of preventative medical endeavours for a whole spectrum of age-related illnesses.

Other major issues

Another significant research field is the intestinal regulation of immunological and metabolic disorders due to nutritional factors. Nutritional components influence the immune system and are therefore of sub-clinical significance. Hence, alimentary-induced inflammatory events play a major role not only in DMT2 but also in cachexia or disorders of the gastrointestinal tract and the immune system. It is equally important to link system-biological metabolic research in future with diagnostics and metabolic disease therapy in line with clinical markers or research geared to hormonal disorders. This is possible now with extensive profiling of metabolic adaptations at mRNA, protein and metabolite level with the aid of high-throughput technologies.

General recommendations

In an international comparison, research on nutrition, metabolism and endocrinology in Germany is in many cases underrepresented for historical and structural reasons. Even though obvious changes have occurred at various research locations in recent years and initial areas of interest have been created, the participation of groups in funding programs of the DFG, BMBF and the EU and the establishment of and involvement in interdisciplinary research networks needs improvement. The same applies to the funding of the next generation of scientists in basic research and clinical-endocrinological research. Programs aimed at funding new talent in basic research in clinical departments dealing with nutrition, metabolism and endocrinology appear to be urgently required. Metabolic and endocrinological diseases affect various organs and organic systems, which were hitherto fragmented and assigned to numerous branches of internal medicine (gastroenterology, hepatology), nutritional medicine, paediatrics, cardiology, and neurology/psychiatry. The age-related diseases resulting from lifestyle as well as from demographics represent multimorbidities, which can only be dealt with through multidisciplinary research efforts. In addition, a closer link is required between fundamental nutritional research at universities and other biomedical disciplines. It is seen as equally important to develop research profiles specific to each location in these facilities and to strengthen them through regional and national collaborations.

2.3. Cardiovascular, lung and kidney diseases

Cardiovascular, lung and kidney diseases are together by far the most frequent causes of death in Germany and other industrialised countries. They lead to a significant reduction in life expectancy and in many cases to a considerable impairment in quality of life for patients over a prolonged period. Coronary heart disease remains top of the list. It is followed by heart failure, which is becoming increasingly serious and affects especially the over-65s. With regard to mortality, incidence and prevalence, disorders of the respiratory tract (including relevant cancers) are immediately after cardiovascular diseases in second place. Just under 10% of Germans suffer from kidney diseases and around 80,000 patients in Germany require chronic kidney replacement therapy. The cost of treatment, care and long-term disability with cardiovascular, lung and kidney diseases takes a substantial amount of health care spending. The incidence and complications of diseases increase steeply as people get older. In view of demographic trends a drastic increase in diseases is anticipated in Germany unless appropriate countermeasures are taken.

Cardiovascular, lung and kidney diseases are often associated with joint risk factors such as diabetes mellitus, overweight, high blood pressure or inhalative smoking. Therefore, they rarely occur in isolation but frequently together, which leads to complex interactions. Besides this, the diseases reinforce each other as they progress. For example, in patients with mild kidney insufficiency the cardiovascular risk rises substantially. This means a patient with kidney disease is a hundred times more likely to die of cardiovascular complications than to need dialysis. Another example is the circulation disorder (pulmonary perfusion) in many lung diseases that produces secondary complications for cardiac function.

There are numerous therapeutic approaches to combat cardiovascular, lung and kidney diseases. Nonetheless, certain methods of treatment (e.g. ventilation, dialysis, transplantation) are only used if serious complications or organ failure have already occurred. However, these laborious and expensive procedures only improve the patient's organ function or overall situation sufficiently and long term in rare cases. Primary preventative approaches are therefore worthwhile and are still urgently required. However, in view of the frequency and considerable distress caused by cardiovascular, lung and kidney diseases, preventative procedures alone cannot improve the health care situation properly in the medium term. The development and funding of concepts geared to early and individualised therapy are thus all the more important.

Against this background, the working group for cardiovascular, lung and kidney diseases has prioritised a number of research topics, which are presented here briefly. A detailed presentation of all the recommended research tasks is included in the full version of the Roadmap report.

Characterisation, regulation and therapeutic benefit of circulatory and tissue constant stem cells

Stem cell therapy is relevant to various diseases of the heart, circulation, lung and kidneys. Improved characterisation of various stem and precursor cells improves our understanding of mechanisms and has great potential for prevention and treatment of the above-mentioned diseases. Germany is already a leader in the development of therapeutic cell strategies to treat heart attacks and heart failure and should improve its position even further. Apart from this, the potential for economic exploitation is estimated as very significant, particularly for small biotechnology firms.

Bio-hybrid organs – organ replacement and tissue engineering

Optimisation of organ replacement procedures through bio-hybrid organs could improve the health care and quality of life for patients and lead to a reduction in treatment costs. In the field of organ support systems great potential exists in a combination of medical technology and methods of tissue engineering, known as a hybrid procedure. German research has many years of experience in this area. Numerous experimental procedures and initial clinical applications are the ideal requirements for further development. This research field offers economic opportunities in biotechnology, pharmaceuticals and medical technology.

Risk prediction and customised treatment

Among the large number of patients who show evidence of risk factors for cardiovascular, lung or kidney disease or are at an early stage of the disease, it is imperative to identify early those for whom progression and the onset of complications are expected. This is because these patients require prompt and effective therapy so their illness does not become chronic and their organ function can be maintained. In diagnostics but also in therapy, advances are achievable with the aid of genetic risk profiles and further progress in pharmacogenetics. This research field is very important as with the findings acquired here a paradigm shift from standardised to customised therapy can be achieved.

Multidisciplinary issues

Molecular diagnostics: imaging and biomarkers

New biomarkers and enhanced imaging procedures could indicate early stages of disease processes or their transformation into a clinical complication and therefore improve the diagnostic possibilities. Applying them is conceivable with var-

ious medical problems, for example, coronary heart disease, heart failure, renal failure, respiratory insufficiency or cancers. German sciences teams have years of experience in this research field and are international leaders. Plus, competitive businesses are already operating in Germany.

Therapeutically applicable molecular target structures: identification and preclinical validation

The identification of new molecular target structures could aid the development of innovative treatment approaches. Several German teams have already identified therapeutically beneficial signalling pathways. Cooperation between teams of scientists and businesses engaged in biomedical research should be encouraged in order to make use of the innovative potential of this work. What is especia

Remodelling including organ fibrosis and reverse remodelling with chronic diseases

Numerous cardiovascular, pulmonary and chronic renal diseases are characterised by structural remodelling processes with the loss of organ-specific cells and structural units and replacement by inappropriately proliferating and/or non-specific cell populations as well as remodelling and increased deposits of extracellular matrix. Organ fibrosis, which may affect vascular and parenchymatose compartments, is a prominent variant of such a remodelling process. The loss of organ function involved with these structural remodelling processes used to be considered irreversible (“fixed”). The concept of “reverse remodelling” describes a paradigm shift with an instruction to reverse these pathological remodelling processes in vivo and thus achieve structural as well as functional regeneration of the organ.

Sub-clinical dysfunction of heart, lung, kidney and metabolic system – risk potentiation due to interactions

The object of research is the interactions in the case of low-level dysfunctions in the cardiovascular system, lung and kidneys as well as metabolic and rheumatic diseases. A better understanding of patho-mechanisms and how they interact would be a decisive step in improving preventative and therapeutic measures. The current network of university hospitals doing research with well organised specialised and rehabilitation departments provides an excellent basis for investigating these issues in Germany.

Other major issues

Another significant research topic is to improve the availability and function of donor organs. Several designated transplant centres, the Human Organ Transplant Act and the German Organ Transplant Foundation have created positive conditions in Germany. Another major research issue is the successful transfer of research findings into clinical practice (translational research), as this may lower morbidity and mortality rates as well as treatment costs.

2.4. Infections, chronic inflammation and inflammatory skin diseases

Infectious diseases and inflammations are a global challenge. While infectious diseases such as malaria, tuberculosis, HIV and hepatitis are still major problems in developing countries, infections among immunocompromised patients are a particular challenge in industrial countries. According to a WHO World Health Report infectious diseases took second place in the figures for cause of death worldwide at more than 26% in 2003. In industrial countries the mortality of infectious diseases is lower due to high hygienic conditions and progress in prevention, diagnosis und control pf infectious diseases. For this reason, they rank third as the cause of death in Germany. However, the morbidity rate of infectious diseases is of huge significance in medical and health economics terms in Germany. In 2006 the Robert Koch Institute registered almost 300,000 notifiable cases of infections. Added to this is an unknown number of unreported cases that should not be underestimated and the large number of non-notifiable and chronic infectious diseases.

Infectious diseases are capable of spreading faster and easier than ever thanks to increasing international mobility. Traditional anti-infective substances (e.g. antibiotics, antifungal agents, virostatics) are losing their efficacy because numerous pathogens are developing resistance against these substances. The number of people who are especially susceptible to infections due to their weakened immune system is rising; these include, for example, the elderly persons and immunocompromised patients with tumours, and transplantees. In addition, infections and inflammations frequently play a role as causal or secondary factors for other diseases such as cancer, aller-

gies or diabetes. As such, several autoimmune diseases and tumours are triggered by infections or inflammations. Against this background, infectious diseases and inflammations will also have great social and economic significance in future and thus impose great challenges on the scientific and health system. Mutations of familiar pathogens (e.g. multiresistant strains of bacteria and viruses) or new pathogens (e.g. SARS, HIV), which have infiltrated the human population due to modern civilisation, also show this clearly.

Intensive research activities in the filed of prevention , diagnosis und therapy of infectious diseases are urgently required. The main research tasks are to analyse the molecular mechanisms involved in developing resistance.in order to identify and develop new target structures for anti-infective substances. There are major shortcomings here as these fields have been neglected for a long time. The shared objective of future research endeavours must be to understand the mechanisms of infectious diseases and chronic inflammations and how they progress and spread. The aim is to develop new, innovative methods and to improve existing procedures that might prevent or combat these diseases. These research issues are of utmost importance for the health care system because they reduce the morbidity and mortality of infections in the long term while delivering strategies to deal with epidemics better in future.

Against this background the team working on infections, chronic inflammation and inflammatory skin diseases has prioritised a number of research topics, which are presented here briefly. A detailed presentation of all the recommended research tasks is included in the full version of the Roadmap report.

Targets for anti-infective therapies

Research has already identified many potential targets for anti-infective drugs (e.g. virulence factors, adhesins). However, the chemical substances that adhere to these structures were unavailable. At present there is a trend towards natural substances in the search for new anti-infective drugs. In addition, immunomodulators are increasingly attracting attention as a weapon against infectious diseases. Even though this involves an important health policy issue, major players in the pharmaceutical industry are turning away from research into anti-infective drugs for economic reasons (market capitalisation is said to be too low); the smaller start-up companies lack venture capital. The integration of chemical and biological/medical ideas could help develop this research field further.

Identification of immunoeffector programs to improve immunoprophylaxis and therapy

The identification and modulation of immune system effector programs to improve immunoprophylaxis and therapy will be of vital importance with acute and chronic infectious diseases in future. Apart from this, these scientific and therapeutic insights can also be used in other medical areas such as cancer, autoimmune diseases, musculoskeletal disorders and transplant medicine as they share the same vaccination principles and the adoptive transfer of stem and immune cell populations. Immunotherapy research is well established in Germany. In the industry immunotherapy and vaccine development are among the fastest growing sectors. There is a need for translational research.

Genetic determinants of susceptibility to infectious diseases

Another very important research issue is the identification of genetic determinants and predispositions, which influence

susceptibility to infectious diseases and chronic inflammations. With genome and proteome research this issue has become more significant and more work is being done on it in Germany too. It provides huge research potential. Its significance for health care and economic exploitation on the other hand is still small.

Multidisciplinary issues**Medical suffering due to infections and the efficacy of population-related interventions – epidemiological study proposals and cross-linking of data**

Intervention studies represent the only possibility of validating theories produced in basic research under the practical conditions of Germany's health care system. Previously, only a few high quality population-based studies of the epidemiology of infectious diseases were carried out. The data available on the effect and efficacy of interventions at population level is inadequate. By employing modern survey and analysis strategies valid data on these issues should be gathered and linked in databases. Population-based studies are also of interest to industry because they serve as the basis for decisions and strategies in developing and launching vaccines and anti-infective drugs on the market.

Development of new animal models

Infectious and inflammatory processes are involved in a large number of diseases, for example, in neurodegeneration, cardiovascular diseases, cancer or autoimmunity and allergies. In many cases it is only possible with the aid of animal models to clarify the cause of complex factors involved in their pathogenesis (e.g. genome environmental interactions). However, for many infectious diseases and non-infectious chronic inflammations no animal models currently exist or are only of limited suitability. The industry is very interested in good animal mod-

els especially to identify drug targets and for preclinical validation studies. It would be worthwhile compiling an overview of the animal models currently available in Germany.

Other major issues

Besides this the scientific team recommends further important research topics in the field of infection and inflammation. This includes identifying non-genetic related risk factors, which influence both the onset as well as progress of infectious diseases. Diagnostic and therapeutic options could be customised and improved in the process. Innovative methods of diagnosing infectious diseases have to be developed and evaluated in clinical practice, as early and specific diagnosis has a crucial influence on the success of treating infections and may prevent late complications. The diagnosis and treatment of organ fibrosis in chronic inflammation processes also needs to be urgently improved. This is an issue that involves multiple organs and medicine disciplines, which is also significant for other research fields (e.g. cardiovascular, lung, kidney and skin diseases).

2.5. Cancers

Cancers are the second most common cause of death in Germany after diseases of the cardiovascular system. Because of the increasingly ageing population their incidence will continue to increase. For some cancers such as leukaemia or certain malignant tumours in children, the chances of a complete cure for patients have definitely improved over the last 10 to 15 years. Also, regarding some common tumours such as breast or colon cancer, the five-year survival rate has increased to over 50%. This positive trend is due to improved diagnostics but also to the implementation of interdisciplinary therapies that include new treatment approaches. Nonetheless, the possibilities for improving the prognosis of cancer patients have still not been exhausted. Further scientific efforts are necessary: the insights acquired in biomedical research must be translated into clinical application, interdisciplinary collaboration improved by creating tumour centres, and individualized tumour therapy taking into account new (molecular) biological findings and biographical and psycho-social aspects.

Only few medical fields other than oncology have created the kind of potential for the transfer of research results into practical applications (translational science). The principles of deregulated growth control with cancers are basically understood. Key molecules and many intracellular signalling pathways, which regulate growth, differentiation, proliferation and cell death, have been identified. The pharmaceutical industry has used these insights to develop new medicines in collaboration with basic research scientists in the last 10 years. These can be deployed as “targeted therapies” in order to repair defective signalling pathways and block deviating signals from being transferred to tumour cells.

Genome research of the last 10 to 20 years has shown that cancer is a genetic disease of the somatic cells. The deciphering of chromosomal changes, translocations and gene amplifications, etc. has led to the development of numerous methods able to diagnose in detail the genetic aberrations in tumours. In addition to our knowledge of genomic changes such as mutations and deletions, findings on aberrant gene regulation via epigenetic regulation have provided new clues about poorly regulated growth control and new therapeutic target structures in tumours.

With the aid of these new molecular procedures, individual tumour diagnostics and therapy is now possible. Previously, oncology medicine was aimed especially at specific organs and therefore allocated to the medical department responsible for the organ in question. In future, oncology will develop into an interdisciplinary area that takes method and application-oriented approaches. To fight disease, conservative treatments of cancers – whether leukaemia, prostate, breast, colon cancer or brain tumour – will become even more important in the future due to new medications that inhibit the transduction of signals or activate the immune system. Individualised, target structure-oriented tumour therapy of this kind will be carried out in interdisciplinary cancer centres, in which operative and targeted drug therapy, radiation therapy as well as immunotherapy are all employed. In order to advance the new therapeutic approaches scientifically, they should be integrated into well structured, representative clinical studies that exploit the entire spectrum of molecular diagnostic and therapeutic possibilities. The basis for this is represented by the well structured therapeutic concepts of the German paediatric oncology and by organ centres and tumour boards in comprehensive cancer centres.

Individualized cancer therapy does not only take account of somatic treatment but also focuses on psycho-oncological aspects such as attending to patients and improving their quality of life. This is particularly important for the increasing number of cancer patients who may not be cured but will still be able to live with their disease for a long time. The interaction between tumour and host organism plays a major role in this.

Against this background the working group has prioritised the following research topics, which are presented briefly here. A detailed presentation of all the recommended research tasks is included in the full version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf).

Migration, invasion, metastasis, tumour stem cells, dormancy

Invasion and metastasis into distant organs are the main clinically relevant problems of cancer. Major issues are associated with tumour cell differentiation – and therefore with the entire tumour stem cell concept – and with the predictability of the time taken for the tumour to progress. The research fields are expected to provide vital impetus for therapy and the findings acquired will be of interest to industry.

Therapy resistance, sensitivity

This research field will also become increasingly important for the health service as well as for industry. This is because identifying and deciphering signal transduction pathways that induce resistance to therapy – i.e. cell death or blocking the differentiation of tumour cells – could form the basis of new approaches to treatment. For this, the development of molecular oriented imaging procedures is required, which can provide an indication of responses to treatment or therapy-induced molecular changes in the tumour.

Tumour host relationship, microenvironment, age, senescence

This issue has great innovative potential as it considers cancer at the superior systemic level rather than as a phenomenon of individual neoplastic cells. The assumption is that better understanding of the basic molecular-biological and genetic properties of tumours and their interaction with the host organism will open up new therapeutic possibilities.

Immunotherapy, gene therapy and tumour vaccination

Immunotherapy is an application-oriented research field of great importance for industrial utilisation. However, “classic immunotherapy” is still not used on patients to the desired extent. With tumour vaccination on the other hand, health care relevant breakthroughs have been achieved, as shown by the development of a vaccine against human papilloma viruses (HPV) to prevent cervix cancer. Antibody-based therapies are also highly relevant for health care. Industry is already achieving considerable sales volumes with these (e.g. Herceptin).⁰

Prolonged survival and consequences of therapy

An analysis of the long-term effects and side effects of medications used to treat tumours plays a major role along with the definition of criteria for quality of life and long-term survival as well as palliative medical issues. Only a few research groups have addressed this issue previously but it has great potential for innovation and will be very significant, both for research as well as health care in future.

*Multidisciplinary issues***Clinical genomics: implementation of diagnostic methods in studies; predictive and prognostic genetic and transcriptional patterns (signatures)**

This issue is also important for other research fields such as cardiology or inflammations, which is why it is classified as multidisciplinary. With the consistent application of “clinical genomics” and the implementation of diagnostic methods and signatures in clinical studies, completely new approaches to tumour diagnostics are emerging. Based on the research findings acquired here, new target structures can be developed and signalling pathways identified. Clinical genomics has been well funded hitherto, and development shortfalls have been definitely reduced – mainly due to resources from the national genome research network (NGFN). Meanwhile, the research findings are also being used by industry. The implementation of results in clinical gene analyses has also improved in recent years. In the future, this research field should collaborate even more closely with clinical research in order to make better use of the material from clinical studies for the development of new treatments.

Innovative imaging

Innovative imaging, in particular functional molecular imaging, is a very important and innovative topic. It also plays a major role in the other working groups and was therefore classified as multidisciplinary. This issue is relevant to industry and the health system. Germany provides much scientific impetus in this research field and is one of the leading countries in it.

Other major issues

Other major issues in cancer research are the development of new surrogate markers and outcome criteria as well as monitoring individual responses to tumour therapy. Both fields

include molecular imaging, therapy resistance, issues of prolonged survival and “clinical genomics”. Aspects of genetic instability, gene regulation, epigenetics and optimisation of local tumour destruction play a role in many of the above-mentioned research fields. Screening procedures and early detection programs should be further developed and evaluated; in Germany there is a lack of evaluation studies particularly. Palliative medicine has been previously neglected by research. Junior training programs could support this project that is exceptionally relevant to the health system. Psycho-oncology and an investigation of complementary treatment procedures could also play a major role in patient care. It also applies to identifying genetic, socio-economic, infection and environmental risk factors for cancer.

General recommendations

In all the proposed topics there are shortfalls in health system-oriented and clinical research. Additionally, basic research should collaborate better with applied research. This would mean for example that a tissue examination in the future would be conducted only on material from clinically well-characterised collectives. Stronger links are also desirable between basic research and other departments such as bioinformatics, in order to gain good impetus.

2.6. Neurological and mental illnesses and diseases of the sense organs

Thanks to increasing life expectancy and changed living conditions neurological and mental illnesses will increase dramatically. This applies equally to stroke, Parkinson's or Alzheimer's disease, depression, addiction and loss of sense organ functions. Today, 27% of Europeans already suffer from a disease of the central nervous system (CNS), in Germany it is almost 32%. Most frequent in this country are anxiety disorders followed by migraine, affective disorders, addiction, psychoses, dementia, epilepsy, Parkinson's disease, stroke, trauma, multiple sclerosis and brain tumours. In 2004 the cost of CNS illnesses in Europe was €386 billion. Mental disorders accounted for most expenditure at 62%, followed by neurological diseases at 22%. Neurological diseases associated with neurodegeneration (e.g. dementia, multiple sclerosis) or secondary loss of nerve tissue (e.g. stroke, diabetic neuropathy), often lead to severe functional impairment for patients. The result is considerable and long-term costs in nursing and health care. The majority of central nervous system diseases are currently incurable and their progress can often only be inadequately treated. The need for targeted curative therapies is therefore considerable. New analytical procedures, which allow for certain and early diagnosis, are also urgently required.

The human brain is probably the most complex organ nature has ever produced. Around a hundred billion nerve cells and far more glial cells form complex linked networks that perform exceptionally every day. Among other things they control our perception, learning, remembering and forgetting and all forms of communication up to and including social behav-

our. In no other organ are nearly as many genes expressed as in the nervous system. Neurosciences have therefore developed into a leading discipline of biomedical research and were significant in elucidating numerous fundamental cellular processes. These include the structures and functions of ion channels, receptors and cell surface molecules, the roles of intra- and extra-cellular second messengers, molecular signal cascades, intra-cellular transport mechanisms. In addition, many control mechanisms for cell growth, cell adaptation, cell survival and cell death plus the integration principles of countless pieces of cellular information within complex cell networks are understood. The next step is to use these basic findings to identify the causes of neurological diseases and mental disorders and translate the results of these investigations into clinical application (translational research). Effective and innovative strategies for diagnostics and the development of causal therapies are needed. This will be the great challenge in decades to come.

Research topics are proposed below on various medical conditions or diseases. The development of causal therapies for these diseases can only succeed long term if basic and clinical research are linked. To this end, six top priority research topics were formulated, which range from molecule to behaviour and usually include animal models for the relevant diseases. These six topics are briefly presented here. A detailed presentation of all the recommended research tasks is included in the full version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf).

Physiology and pathology of synaptic processes

With this topic the focus should be on an examination of pathological changes in synapses (synaptopathies). Numerous

diseases such as schizophrenia, depression and epilepsy are associated with synaptopathies. Even if the physiological processes with synapses including the basic molecular mechanisms are already well understood, an investigation of the causes and consequences for the respective disease is urgently required. The focus of future research endeavours should be on interdisciplinary cooperation between basic and clinical research teams. Suitable animal models have to be developed, which enable an investigation of various disease-specific issues. In view of the rapid development of this research field, major findings are expected in the foreseeable future, which can flow into drug development.

Neurobiology and psychobiology of aggressive, impulsive and addictive behaviour

The health and socio-political relevance of errant behaviour cannot be rated highly enough. This topic encompasses a wide area of research into the basics of behaviour and its pathological disorders. The advances of recent years particularly in method development, e.g. in functional imaging, will permit for considerable progress in this research field. Of specific scientific interest is the onset of aggression in its early forms. Future research should focus on interdisciplinary cooperation of different departments (genetics, neurology, psychiatry and psychology) as well as translational aspects. Once again, suitable animal models must be developed, which enable a direct analytical research approach.

Early diagnosis of neurodegenerative diseases

This topic includes degenerative processes in neuronal diseases and the regulatory processes controlled by them. Apart from various other neurodegenerative diseases dementia is regarded as significant and in view of demographic trends it has priority socio-politically and economically. There is a

need for research in the field of structural biology and molecular mechanisms of protein aggregations. The results of this research are required immediately to improve early diagnostics. Based on the knowledge of pathogenetic mechanisms, it is equally important to identify and validate biomarkers. As long as the risk factors for dementia are unknown, no effective therapeutic guidelines can be developed and applied in the health care system.

Neurosensorics

Neurosensorics encompasses “Degenerative retinal diseases” and “Sensorineural hearing loss and vestibulopathy”. The sensory systems to be examined (eyes, ears/vestibular organ) work in closely related ways. With various diseases a common genetic basis for disordered transduction processes of both sensory systems is available. Accordingly, the comorbidity of sensory diseases is very high. Research questions regarding receptor mechanisms or central processes are generally quite similar. For both sensory systems the peripheral transduction mechanisms are well-researched and viable animal models exist. An acute research need exists in the development of diagnostic instruments and therapeutic approaches. Gene therapy approaches also appear promising. Greater cooperation between surgical and neurological/internist oriented researchers is desirable in terms of finding new therapeutic options. For the development of neuroprotheses close contacts are necessary with medical engineering. Strong potential exists here for industrial development (SME) and exploitation.

Age-related functional brain development and disorders with regard to learning and memory processes

“Neurobiology and pathology of learning and memory” and “Structural and functional brain development and its disorders” were combined. Processes of learning and memory

formation involve structural changes in the brain, which are also observed at various stages of the brain's development. In addition, developmental disorders and learning and memory disorders are probably due to the same pathological mechanisms. This topic encompasses not only (early) stages of childhood development but all age groups. Even in the brains of older people neurogenesis occurs in regions that are relevant to learning and memory and therefore a repetition of certain developmental processes.

Research tasks have to do with human learning especially. For an understanding of the pathogenesis of developmental and learning processes the development of suitable animal models is required. Advances are also expected from further developments in genetic imaging methods. Germany's research scene is very well positioned in the cognitive research field particularly, but it is too small. Only a few centres exist that pursue memory research in humans or primates. In the neuropaediatric field there are also shortcomings. Research has to be extended particularly on infant development and the problems of premature births. On the subject of learning and memory at all ages prospective long-term studies are required.

Neurostimulation and neurobionics

“Neurobionics” and “Basics of neuromodulation through stimulation” treat different aspects of the same research field. They are characterised by the issues and technological problems they share. This is a very new, explosively developing field that benefits from both advances in methodology and findings in neurosciences as well as material research and nanotechnology. This is why greater cooperation between these disciplines is required. German research teams are very well established in the technological field and with regard to non-invasive therapeutic procedures. However, in the long term the

use of invasive techniques (invasive neuroprosthetics and neurostimulation) in humans will be unavoidable. There is a lack of the necessary basic animal experimental tests with the aid of neuroimaging. Furthermore, technological aspects have to be included more in research issues, in order to improve transfer of research findings into industrial applications and utilisation works.

Other major issues

Another important health policy issue is chronic, therapy-resistant depression. The above-mentioned topics include various research questions on depression and affective disorders: e.g. depression is among the illnesses where synaptic functions are pathologically changed. Learning and memory processing disorders are also observed in patients with depression.

Interactions between the immune and nervous system are increasingly becoming the main focus of research interest in various processes of damage, regeneration and protection of the central nervous system.

In order to develop innovative therapies for vascular diseases of the brain and sense organs the pathogenesis of microangiopathies has to be clarified further.

Investigating the chronic progress of pathological sensations such as pain and tinnitus requires increased efforts to prevent an acute sensory information becoming a chronic, pathological one.

General recommendations

For the field of neurology, psychiatry and sense organs and others the following obstacles to research in Germany have been identified:

- Basically, attention has to be focused on creating greater scope for clinical basic research. It also includes a solution to the problem of different remuneration rates for doctors and medical researchers.
- In the clinical research field there is a lack of funding instruments for long-term maintenance of population-related databases and biobanks and auxiliary structures such as the Telematikplattform für medizinische Forschungsnetze e.V. (TMF). There is also a lack of suitable funding instruments to conduct long-term studies. The potential for transfer of findings from research to industrial utilisation is too often not recognised promptly or not used at all. New biomedicine technology study courses, which train and promote qualified junior staff, must be established and should include this aspect. (Neuro) Imaging methods play an increasingly important role in addressing various research issues, including animal experiment research.

2.7. Multidisciplinary issues

The working groups and the coordinating group have identified several multidisciplinary issues overall, which are relevant to several of the six medical fields. They are combined under the categories of “clinical method development”, “multi-organic translational research” and “health service research” (see Table 2, page 10).

A detailed presentation is included in the form of definitions of issues in the full version of the Roadmap report (available only in German: http://www.gesundheitsforschung-bmbf.de/_media/Roadmap-Bericht.pdf).

Clinical Method Development

Conducting **long-term studies** both for clinical as well as **epidemiological issues** has been considered especially urgent along with creating and maintaining population-based **databases and biobanks** long-term and **auxiliary networking structures** such as the Telematikplattform für medizinische Forschungsnetze e. V. (TMF). A major gain in insights is anticipated from clinically and/or genetically well characterised patient cohorts. Major potential has been identified in further development of **innovative imaging**. Imaging procedures play an outstanding role in modern health research because they are deployed in a variety of ways in deciphering pathomechanisms and in clinical, patient-oriented research. They are also becoming increasingly important in animal experiment research. Large scale imaging equipment is available for use at university hospitals usually in radiology departments, which in many cases do not provide sustained support to the research of other departments – especially if they are not significantly involved in relevant projects. In the process insights into health care and experiments on behalf of the medical engineering industry are

prioritised ahead of other research interests. In the main there is a lack of interest-balancing decision procedures on the use of large imaging equipment at university hospitals.

Molecular diagnostics with imaging and biomarkers aims to develop disease-specific marker molecules, ligands for these molecules and to develop suitable imaging procedures to visualise their interaction and ultimately the clinical validation of these procedures. It is supposed to allow for earlier diagnosis of diseases and an assessment of their course. Applying them is conceivable for various diseases.

Clinical genomics including transcriptome and proteome analysis offer outstanding opportunities for the development of new test procedures, e.g. to specify new molecular markers and to develop new, more targeted therapeutic agents. With modern high throughput procedures tumour entities can be better defined at molecular level, for example, and relevant sub-groups identified for prognosis. However, the prognostic relevance of molecular markers has to be validated in study collectives of (tumour) patients.

Translational research – i.e. research at the transition point from preclinical to clinical should play a major role in future. As such, procedures will be applied especially whereby conclusions can be made about the possible chances of success for a substance or a therapeutic or diagnostic procedure in the clinical field. These include both investigations in the preclinical field (cell cultures, animal models) as well as clinical testing in the form of phase I to phase II studies. Apart from this the term includes the implementation of research results in a product or procedure and cooperation with industry as well. Essential issues here are the **identification of target structures that can be used in therapy and clinical studies to evaluate**

molecular diagnostic methods as well as predictive and prognostic genetic and transcriptional patterns (signatures).

Multi-organic translational research

Disease-specific animal models allow for the analysis of pathogenic mechanisms behind human diseases. With their help great progress is anticipated in understanding human diseases as well as target identification and preclinical validation of potential therapeutic or preventative agents. However, with many diseases there are currently no animal models or only those of limited suitability. From the industry's perspective there is great interest in this research field; the focus here is on proof-of-concept. Often there is no overview on hitherto available or accessible animal models, their conclusions and their limitations. The proven skills in Germany along with a sufficient number of working groups in the field of model organisms are a very positive prerequisite for further development in this field.

Numerous cardiovascular, pulmonary and renal diseases are characterised by structural remodelling processes with the loss of organ-specific cells and structural units and increased deposits of extracellular matrix (remodelling). Organ fibrosis, which may affect vascular and parenchymatose compartments, represents a significant version of this kind of remodelling process. The loss of organ function associated with these structural remodelling processes were previously considered irreversible ("fixed"). The concept of "reverse remodelling" describes a paradigm shift with an instruction to reverse these pathological remodelling processes in vivo and thus achieve structural as well as functional regeneration of the organ.

Organ regeneration through stem cells is a highly relevant issue with major development potential for many research

fields from cancer research and cardio-vascular / pulmonary / renal research, musculoskeletal system research to endocrinology. The major concern here is an understanding of the molecular regulation of stem and progenitor cell differentiation and proliferation in the development and regeneration of tissue. Comprehensive knowledge of all the genes and signalling paths involved is required for specific control of tissue regeneration through stem cells.

Cell ageing is a major issue both for the onset of cancer as well as for degenerative diseases, such as of the musculoskeletal system or the central nervous system (CNS). Cellular ageing and mitochondrial energy metabolism also represent a major mechanism in the pathogenesis of obesity and diabetes. The loss of specialised, hormone-producing cells is often the cause of hormonal diseases.

The increasing molecular definition of disease processes may enable molecular risk prediction for individuals, which allows for risk patients to be identified and have customised diagnostics, therapy and maximised therapy. This prevents unnecessary treatments on low risk patients and unnecessary stress at the same time. This is a core issue in international research, to which significant economic potential is attributed both for the development of new treatments as well as early diagnostic methods and lab diagnostics.

Health service research

Research for the transfer and implementation of new scientific findings in routine health care have been given significant status, as a great discrepancy exists between the state of knowledge and application in clinical practice. This branch of research has been neglected too much in the past or else not pursued as it needed to be. The relevant research findings that

would lead to implementation of evidence based therapeutic principles in routine practice would be very effective in improving the actual health care situation. An important parameter that has to be considered here is the frequent multimorbidity in chronic diseases, so that a singular organ-related therapeutic approach does not do enough in many cases.

When treating chronic diseases **complex multimodal therapeutic concepts** are often employed. However, they are based mostly on expertise that is solidly backed particularly under routine medical care conditions only to a limited degree. An evaluation of therapeutic procedures has always been largely determined by industry interest in the past (e.g. Phase III/IV studies on new medications). Internationally this is an expanding field of enormous interest for health policy and growing economic significance. Germany is among the leading research nations albeit on a minor scale – which is why this field is regarded as capable of expansion.

Palliative medical research enables innovations for a disease stage that was not a focus of medical research in the past. For patients and family this may contribute greatly to significant relief in what they are going through in the final stages of life. This is where obstacles such as sector-related organisation, a lack of research and training and further training among doctors and nurses may have a direct and noticeable effect on patients. It is thus expected that advances in this field may soon bring an improvement in health care in their wake. Research into the psycho-social and spiritual health care as well as decision-making mechanisms and limitations of present health care infrastructure may be significant in diseases that lead to death for many but also non-life-threatening ones if their progress is chronic.