

Federal Ministry of Education and Research (BMBF)
Call for Proposals
Guidelines for Funding Systems Biology in Cancer Research

1. Purpose of Funding, Legal Basis

1.1 Purpose of Funding

The development and course of many diseases is determined by the complex interaction of numerous molecular factors. Detailed basic findings on factors that determine diseases and advances in new diagnostic technologies are decisive for the development of personalized medicine for individual patients or particular patient groups. Personalized medicine can bring about fundamental changes in health care. Measures for prevention and early diagnosis that are optimized for each patient can help prevent diseases and make their course less severe. Customized drugs help make treatment more effective and reduce troublesome side effects.

The basic mechanisms of diseases must be understood and the molecular interfaces that play a part in their manifestation identified before personalized medicine is possible. The findings of basic research in the life sciences by high-throughput techniques and innovative chip technologies already allow a large amount of clinically relevant data to be collected and analyzed. A wealth of information relevant for individualized treatment can be gained in this manner.

However, genome research reaches its limits in understanding the mechanisms of the interplay between genes and their products and the interaction between the genome and its surroundings. The systems biology approach is considered promising for a holistic understanding of the behaviour of complex biological systems and diseases as well as of the effects of changes on the system. The components of a biological system and their interactions are quantitatively analysed and the data are mapped onto models using mathematical concepts. These models increasingly enable researchers to simulate and predict disease-relevant processes in human cells, tissue and organs. It is to be expected that in particular multi-factorial diseases such as cancer will, in the future, profit from systems biology.

For example, system biology models can be used to specifically map disease processes including all relevant key molecules and events in the complex aetiopathogenesis of cancerous diseases. This has already proven successful in some cancer-relevant areas. Initial mathematical models have thus been developed that describe, for example, the interactions of various molecules in cancer pathogenesis (signal pathways).

New high-throughput technologies for the structural and functional analysis of the genome together with research approaches of systems biology have provided the potential for more specific diagnosis capable of detecting cancerous diseases at an early stage as well as for assessing disease activity and progression. In future, this will permit considerably more selective treatment, which will therefore be better and more cost-effective. This facilitates the next step from clinical diagnostics (past) via technical and instrumental diagnostics (present) to a molecular definition of disease processes (future).

The Federal Ministry of Education and Research (BMBF) therefore intends to fund “Systems Biology in Cancer Research” (CancerSys). The funding measure aims at causing a paradigm shift from universal standard treatment to individualized treatment by utilizing the potential of systems biology for cancer research, at supporting the development of new drugs with the help of predictive models, and at using new activation profiles (transcriptomes, proteomes) and biomarkers for early diagnosis methods as well as laboratory and pharmacogenetic diagnostics. For this purpose, algorithms, models and software must be developed and/or optimized in order to analyse the effects of complex patterns of regulation, networks, interaction, proteomes and genes.

1.2 Legal Basis

Projects can be funded in accordance with these guidelines, BMBF’s standard terms and conditions for grants on an expenditure or cost basis, and the administrative regulations supplementing Articles 23 and 44 of the Federal Budget Code (BHO). Applicants have no legal right to receive funding. The funding agency will make a decision after duly assessing the circumstances within the framework of the budget funds available.

2. Projects to be Funded

Funding is available for interdisciplinary research collaborations (engineering, computer sciences, mathematics, chemistry, biology and medicine) in order to create effective synergies between systems biology and cancer research. Innovative questions of systems biology in cancer research should be worked on in model-driven approaches. The collaborations should be thematically focused, and knowledge may be gained in diagnostics as well as in tumorigenesis or for example metastasis.

Experimental, clinical and theoretical working groups from university, non-university and industrial research institutions should form collaborations on a regional or national level and thus pool the required expertise and available resources. Individual projects that are not part of a collaboration will not be considered. The proportions of theoretical (e.g. mathematical modelling, bioinformatics), experimental (e.g. molecular biology, cell biology, genetics, biochemistry) and clinical components (e.g. oncology) must be designed to be balanced in the project. Further disciplines (e.g. theoretical physics, biostatistics) may be included as required by the individual research topic. The collaborations are intended to be funded for a period of three years, and a two-year extension may be possible.

Funding is provided for:

- Model-based studies to establish and validate cancer-specific marker molecules (biomarkers) which, for example, facilitate earlier diagnosis as a basis for measures of prevention or early treatment, or the prognosis and monitoring of the course of a disease or the success of treatment. The type of biomarker must be clearly defined (e.g. an individual gene or protein, the genome of a tumour, or a pattern of proteins, gene mutations or metabolites), and the biomarkers should contribute to a systems understanding of cancerous diseases.
- Based on detailed knowledge, for example of the expression and protein profiles of certain types of cells/tumours or the metabolic changes in tissues, models for predicting effectiveness and specificity (pathway analyses) can be

developed for new and existing active substances/drugs on different cancer forms and individuals (e.g. age-dependent effectiveness).

- Investigations on the systemic understanding of the interaction between the tumour and the “host”: beyond the investigation of the tumour system, its environment (surrounding connective tissue, immune system, organ specificities, individual metabolism) must also be considered, because this influences whether the tumour forms metastases or not, for example. This includes the study of tumour initiation as well as the influence of the immune system and age on tumorigenesis as well as the role of stem cells in this process.
- The validation of *in silico* models with experimental and/or clinical data from pathophysiologically relevant animal models or well-characterized and standardized patient and data material is essential.

Research projects from the following areas are not eligible for funding:

- pure cancer research or descriptive statistics studies
- clinical trials
- investigations to develop new forms of drug administration
- projects for developing general procedures (methodological basis) or modifying existing procedures
- *de novo* installation of research resources and infrastructure, in particular, new collections of material
- studies on the clinical value of *in vitro* diagnostic products that are already on the market

2.1 Data Management

As in existing funding measures, it is planned to establish a centralized data management. The necessary additional financial resources will be made available by BMBF in accordance with the assessment basis for grants (see section 5).

The central data management is designed as a service for all projects supported within the framework of these funding guidelines. Participation in central data management will be mandatory for all projects. The objective is to standardize experimental data and mathematical methods and models so that they can be used as widely as possible. Applicants must therefore possess verifiable expertise in the communication and harmonization of documents such as quality manuals and standard operating procedures (SOPs), in ensuring access to these materials, and in organizing interdisciplinary working groups. In addition, relevant preliminary work on the topic and identifiable know-how in data management, databases (production, maintenance, safety), other information technologies (communication platform, online forums, document administration, hierarchical structures) and public relations work are also required.

3. Grant Recipients

Organizations eligible to apply for funding are institutions of higher education, non-university research establishments, and commercial companies with their headquarters in Germany, particularly SMEs (the European Community's definition of SME can be found at: http://ec.europa.eu/enterprise/enterprise_policy/sme_definition/index_de.htm).

Research institutions that receive their basic funding jointly from the German Federal Government and the federal states will only be granted project funds supplementing their basic funding for their additional expenses under certain conditions.

4. Prerequisites for Funding

For potential biomarkers, there must be results from basic cancer research which suggest that a tumour genome/mutation/protein/gene has the potential to act as a diagnostic or prognostic biomarker either on its own or in combination with other tumour genomes/mutations/proteins/genes. These preliminary results must be proven (publications or patents). During the application process, the patent situation for the marker to be validated and the verification methods used must be clarified and described in the application, if applicable.

The heart of the systems biology approach is an iterative process between laboratory experiments and mathematical modelling using computers. Based on large volumes of quantitative data, algorithms are used to create models which allow predictions to be made of the behaviour of complex biological systems with the aim of gaining an overall understanding of the system. The necessary prerequisites for generating a large amount of quantitative data (genome, transcriptome, proteome) must be provided.

The topics chosen must be dealt with according to the conceptual approach of systems biology in accordance with section 1.1. This means that the partners must develop solutions and derive predictions in an iterative process consisting of experiments, data analysis and computer modelling in close interdisciplinary cooperation. Every project proposal or application should therefore explain how the data and their acquisition will be standardized within a collaboration.

Collaborations must be willing to consistently work with and adhere to defined standards that combine experimental work and mathematical modelling.

In order to work on the mentioned issues in a targeted manner, collections of clinical material (cells, tissue, blood, DNA, and, if required, whole organs, etc.) and the associated clinical data of the test persons (patient cohorts with comprehensive clinical characterization) must be available and accessible. Collections of materials should be built and maintained with SOPs for isolation, transport, processing, storing and further use and the previous usefulness of these collections should be demonstrated by relevant publications.

It is expected that grant recipients will set up their own scientific platform for internal and external communications (e.g. annual workshops, scientific events) and that they will participate in scientific events organized within the scope of other BMBF research and funding initiatives on systems biology. This scientific platform can be established in connection with the central data management.

In their own interest, applicants should familiarize themselves with the EU RTD Framework Programme when planning a national project. They should check whether the envisaged project has specific European components so that funding from

exclusively EU sources is possible. Moreover, it should be verified whether, in the context of the planned national project, an application for supplementary funding can be submitted to the EU. The result of such examinations is to be briefly described in the application for national funding.

Since collaborative projects will be funded, a joint application of the interested parties is required. The partners in a “collaborative project” must regulate their cooperation in a cooperation agreement. Before a funding decision can be made, proof of basic agreement on specific criteria set by BMBF must be furnished. Details can be found on a BMBF information leaflet – Form 0110 – (<http://www.kp.dlr.de/profi/easy/bmbf/pdf/0110.pdf>).

5. Type, Scope and Amount of Grant

Funding may take the form of non-repayable grants awarded for projects. Projects should be designed to last for a period of three years.

Funding may be granted for project-related extra expenses, such as personnel costs, equipment and travel expenses as well as investments in connection with the project if they are not part of the applicant's basic equipment.

The basis for calculating the grants for industrial companies is the eligible project-related costs of which, as a rule, up to 50 % can be financed, depending on the closeness to application of the project. BMBF policy requires that the organizations make an adequate contribution of their own – in principle, at least 50 % of the total costs eligible for funding.

The basis for calculating the grants for universities, research and scientific establishments and comparable institutions is the project-related expenditure eligible for funding (the eligible project-related costs in the case of Helmholtz Centres and the Fraunhofer Society (FhG)), up to 100 % of which can be funded in individual cases.

The European Commission's Community Framework for State Aid for Research and Development (FEul grants) must be observed when fixing the rates for funding. This Community Framework permits differentiated extra percentage points for small and medium-sized enterprises (SMEs), which may lead to a higher rate of funding.

6. Other Terms and Conditions for Awarding Grants

The General Auxiliary Terms and Conditions for Funds Provided by BMBF to Commercial Companies for Research and Development Projects on a Cost Basis (NKBF98) will be an integral part of the conditions of award for grants on a cost basis.

The General Auxiliary Conditions for Grants for the Promotion of Projects (ANBest-P) and the Special Auxiliary Terms and Conditions for Grants from the BMBF for the Promotion of Projects on an Expenditure Basis (BNBest-BMBF98) will be an integral part of the conditions of award for grants on an expenditure basis.

7. Procedures

7.1 Commissioning a Project Management Organization and Request for Documents

BMBF has authorized the following project management organization to implement the funding measure:

Project Management Jülich (PtJ-BIO)
 Biology Division
 Forschungszentrum Jülich GmbH
 D-52425 Jülich
 Tel: +49 2461/61-5543
 Fax: +49 2461/61-2690
 Internet: <http://www.fz-juelich.de/ptj>

Contact:

Dr. Christian Eder
 Tel: +49 2461/61-3254
 Email: c.eder@fz-juelich.de

It is recommended that applicants should contact Project Management Jülich for advice in filing applications. Further information and explanations can be obtained there.

Forms for funding applications, guidelines, information sheets, instructions and auxiliary terms and conditions can all be found online at <http://www.kp.dlr.de/profi/easy/bmbf/index.htm> or copies can be requested directly from Project Management Jülich.

It is recommended that the “easy” electronic application system (<http://www.kp.dlr.de/profi/easy/>) be used for compiling project outlines and formal funding applications.

7.2 Funding Procedures

The funding procedures consist of two stages. However, there will only be one review by external experts.

7.2.1 Submission and Selection of Project Outlines

In the first process step, project outlines should be sent by post to Project Management Jülich in a written and electronic form (using “easy”, (<http://www.kp.dlr.de/profi/easy/skizze/index.html>) **by 01.10.2010 at the latest**. The project outline should be submitted by the collaboration coordinator. Each collaboration should submit one unbound copy in written form. The electronic version of the project outline can be submitted as an unprotected PDF or Word document (e.g. on a CD).

Since an international appraisal procedure will be carried out, it is recommended that project outlines should be submitted to PtJ-BIO in English.

The deadline for submitting applications is not a cut-off deadline. However, it may not be possible to consider project outlines received after the specified date.

The project outlines should be structured as follows:

1. subject and objective of the project
2. specific contribution of the project to the funding measure “Systems Biology for Cancer Research”; project outlines regarding central data management must be marked as such
3. state of the art, applicants' previous work, if applicable, patent situation and economic significance
4. participating partners from science and industry (if applicable) and their expertise
5. structure of research core or cooperation project, project management/coordination
6. detailed description of the three-year scientific concept including the financial framework (in tabular form)
7. strategy for data management and data standardization
8. utilization plan with time horizon
9. need for funding

Project outlines should be no longer than 20 A4 pages. Longer outlines will not be taken into consideration. Project outlines that do not meet the formal requirements will not be considered in the review procedure. The cover page and the table of contents do not count as a page. Citations from the literature and figures must be included in the 15 pages and cannot be appended. CVs need not be submitted.

No legal claim to funding can be derived from the submission of a project outline.

The project outlines received will be evaluated with the involvement of external experts according to the following criteria:

- relation to the funding measure
- scientific and methodological quality, innovative contribution and prospects of success of the overall project
- preliminary works and scientific quality of the individual subprojects
- clear focus on a superordinated research question integrating all subprojects
- integration of all relevant (if applicable, interdisciplinary) expertise and facilities (or efficient access to such facilities) in a synergistic research cooperation
- quality of the project partners' interdisciplinary cooperation with respect to the systems biology approach
- quality of data standardization
- demonstrated availability of adequate resources, in particular, relevant and clinically well-characterized patient and control material in sufficient quality and quantity (if required)
- transfer of research findings, possibilities of utilizing research results

For Outlines on Central Data Management:

- methodological quality, innovative contribution and prospects of success of the overall project
- previous work
- quality of the concept for integration of overall interdisciplinary collaboration with respect to the systems biology approach
- quality of the strategy/concept for data management
- quality of the scientific platform concept for internal and external communication

The project ideas suitable for funding will then be selected on the basis of this evaluation. Applicants will be informed in writing about the result of the selection process.

Applicants have no legal claim regarding the return of their submitted project outlines.

If necessary, these guidelines for funding will be used as the basis for further selection rounds. The deadlines for submitting project outlines will be published in good time at <http://www.fz-juelich.de/ptj/systembiologie>.

7.2.2 Submission of Formal Funding Applications and Decision-Making Process

In the second stage of the process, those candidates whose project outlines have been positively evaluated will be requested to submit a formal application for funding in cooperation with the envisaged collaboration coordinator. This will form the basis for the funding decision, which will be made after a final review.

Approval, payment and accounting of the funds, as well as proof and examination of proper use and, if necessary, revocation of the award and reclaiming of the funds awarded are governed by the administrative regulations pertaining to Article 44 of the Federal Budget Code (BHO) and Articles 48 to 49a of the Administrative Procedure Act (VwVfG) unless the present funding guidelines permit an alternative procedure.

8 Entry into Force

These funding guidelines will enter into force on the day after their publication in the Federal Gazette (Bundesanzeiger).

Berlin, 09.07.2010

Federal Ministry of Education and Research (BMBF)

On behalf of

Prof. Dr. Frank Laplace