

Federal Ministry of Education and Research
Announcement of Funding Guidelines
for Project Ideas as Part of the Measure
“Research Network Systems Medicine of the Liver - LiSyM”

1. Purpose of Funding, Legal Basis

1.1 Purpose of Funding

About five million individuals are affected by liver diseases in Germany. The causes of these diseases often remain unknown, despite the enormous progress made in terms of their treatment. The elucidation of the fundamental mechanisms underlying liver diseases and the development of new treatment approaches are therefore of great importance and, at the same time, they pose a great challenge to the public health care system.

The Federal Ministry of Education and Research (BMBF) has used the approach of systems biology to address this challenge as part of its biotechnology programme entitled *Biotechnologie – Chancen nutzen und gestalten. The Virtual Liver (VLN)*, a competence network funded since 2010, studies a variety of physiological processes of the liver, such as fatty degeneration, regeneration, and inflammation using the systems biology research approach. In so doing, it builds on the progress made in the funding measures *HepatoSys* and *HepatoSys2*. The aim is to develop multiscale mathematical models that can be used to describe the physiology, morphology, and function of the human liver. Applying the systems biology research approach to an entire human organ for the first time means that the network carries out pioneering work in the area and is therefore considered to be unique in the world. The multiscale models generated in the *VLN* thus enable a holistic understanding of the liver, from individual cellular processes to the anatomy and function on the level of the entire organ. Initial approaches to paving the way for the clinical application of these findings have already been developed. Further information on the competence network is available on the Internet at www.virtual-liver.de.

With the funding measure *Research Network Systems Medicine of the Liver – LiSyM (Liver Systems Medicine)* the systems biology approach, i.e. the interaction between biological experiments and mathematical modelling, is to be transferred to application-oriented liver research as a next step. The methodological and technological platform of the *VLN* will be used to cover the existing demand for research in this area and to employ computer models in clinical application on a widespread basis for the first time. To this end, funding will be granted to interdisciplinary networks of physicians, molecular biologists, and bioinformaticians.

The overall goal of the *LiSyM Research Network* is to identify and model the common key processes that lead to liver diseases. In order to use the understanding of these processes to develop novel treatment and prevention approaches, disease-relevant and, if possible, personalized multiscale models are to be derived. For the first time, these models will be based on a holistic understanding of the liver and will translate the extensive knowledge on all scales of this organ into tangible improvements for each patient as an individual. Based on current progress in clinical liver research, this approach is to enable early treatment, which can prevent these diseases from becoming severe.

The implementation of this funding measure supports the goals of the research and funding concept *e-Med: Paving the Way for Systems Medicine* in the module “Future-Oriented and Cross-Cutting Measures” and sets overarching impulses for reaching the goals in the fields of action “Focussed research into major diseases”, “Individualised Medicine”, and “Research into Prevention and Nutrition” in the *Health Research Framework Programme of the Federal Government* (http://www.gesundheitsforschung-bmbf.de/media/Gesundheitsforschungsprogramm_engl_barrierefrei.pdf).

1.2 Legal Basis

Projects may be funded by grants in accordance with these guidelines, the BMBF’s standard guidelines for grants on an expenditure or cost basis, and the administrative regulations concerning §§ 23 and 44 of the Federal Budget Code (BHO). Applicants have no legal claim to funding. The funding body will make a decision at its own discretion within the scope of the available budget.

Funding for applicants engaged in economic activity is as a rule state aid in accordance with Article 107 of the Treaty on the Functioning of the European Union (TFEU). In these cases, the grants will be provided as individual aid in accordance with Article 3 Para. 2 of European Commission Regulation No. 800/2008 of 6 August 2008 declaring certain categories of aid compatible with the common market in application of Articles 87 and 88 of the EC Treaty (General Block Exemption Regulation – GBER) (published in the Official Journal of the European Union L 214 of 9 August 2008, p. 3), and are subject to the restrictions in Article 31 GBER. They are therefore compatible with the common market under Article 107 Para. 3 TFEU and exempt from the notification requirement in Article 108, Para. 3 TFEU (http://www.bmbf.de/pubRD/agvo_gesundheitsforschung_gesamt.pdf).

In accordance with Article 1, Para. 6, point (a) of the GBER, any enterprise subject to an outstanding recovery order following a previous Commission Decision declaring an aid illegal and incompatible with the common market is not eligible for individual aid.

These funding guidelines apply in conjunction with the *Health Research Framework Programme of the Federal Government* (http://www.gesundheitsforschung-bmbf.de/media/Gesundheitsforschungsprogramm_engl_barrierefrei.pdf).

2. Projects to be Funded

The *LiSyM Research Network* is a funding measure that builds on knowledge gained in the *VLN*. Mathematical models of different physiological processes in the liver on different scales have already been developed in interdisciplinary cooperation. By means of so-called “showcases” related to specific diseases, research activities within the competence network were pooled and focused. This structure has proven to be promising and will be used again in this scheme to bundle research results and enable their exploitation for medical applications. In particular, this requires close cooperation with clinicians in order to create efficient synergies between systems biology and clinical liver research.

Funding is available for joint projects that focus on overarching, medically relevant questions and which have a good starting position (clinical data and models). The knowledge gained may concern both the development of liver diseases and the field of diagnostics, or the development of new treatment options. To this end, experimental and theoretical research groups should join forces on a

regional or transregional level with at least one clinical research institution to pool the necessary expertise and available resources. Individual projects that are not part of a collaboration will not be considered. The contribution from theoretical research (e.g. mathematical modelling, bioinformatics) and experimental research (e.g. molecular biology, genetics, biochemistry) must be balanced in the project plan. In accordance with the purpose of funding, it is mandatory to integrate expertise from the clinical field. Additional disciplines (e.g. theoretical physics, biostatistics) may also be incorporated depending on the requirements of the research question.

Funding for early-career scientists as heads of young investigators groups is possible under the *LiSyM Research Network*. Preferably, these groups should be integrated into joint projects and independently carry out part of the cooperative work. On the basis of the collective salary agreement currently in force, for the eligible period it is possible to provide project-related funding for the position of the leader of a young investigators group with up to salary grade E14 of the Collective Agreement for the Civil Service (TVöD), up to one position in salary grade E13 TVöD (postdoc) and up to two positions in grade 13/2 TVöD (PhD students) for other scientific personnel, as well as the necessary technical staff if applicable. Equivalent medical staff can also receive funding for all of these positions. Expenditure for equipment and investments and travelling expenses will be reimbursed according to the provisions of the other terms and conditions currently in force for the awarding of grants. Young investigators groups are usually funded as individual projects.

The individual joint project with the associated young investigators groups are integrated into a larger research network, each forming national nodes that work on specific medical questions and that are modelled according to the showcase structure. Collaborations between the individual cooperations or nodes are desirable in order to utilize existing resources effectively, thus supporting the network. In the selection of the projects, the applicants' willingness to integrate their own project into an overall strategy for building and organizing the *LiSyM Research Network* will therefore play a decisive role.

The *LiSyM Research Network* has the character of a pilot project that will serve as a model for the establishment of future systems medicine centres that are considered to have a high potential for the solution of future health-relevant problems.

The research activities of the collaborations should be guided by the following overarching scientific questions and challenges:

- link between systems biology research and a clinical environment with comprehensive expertise in researching liver diseases
- elucidation and modelling of common key processes that lead to liver diseases
- identification of possible targets for new drugs, development of prognostic biomarkers, new intervention strategies, and approaches for prevention
- generation of standards that allow research results to be applied in medicine
- development of innovative, multiscale modelling approaches that can be utilized in a medical environment
- validation of the results from experimental research using clinical data
- organization of simple, fast, and multiple access to patient data
- establishment of a central data management system for an open exchange of protocols and data within the research network

- use of methods and expertise of medical informatics for the evaluation of medical data and clinical application of computer models within the legal framework

All the data collected and models developed will be made available within the *LiSyM Research Network*. A central data management system will therefore be established. Links with existing data management systems in systems biology will be welcomed.

Successfully dealing with the complex, multidisciplinary issues in the *LiSyM Research Network* requires particularly intensive and efficient cooperation of all the working units involved. In order to ensure this, a programme management is to be set up based on the experience in the *VLN*. This programme management will support the control of the entire network, and, together with the project leaders, it is responsible for a regular exchange of information and the coordination of activities. It is also expected that it will set up its own platform for internal and external scientific communication (e.g. annual workshops, meetings of PhD students, cooperation meetings).

At the deadline for submitting project outlines, an implementation concept must also be submitted with a dedicated budget for the programme management of the *LiSyM Research Network*.

With respect to the framework conditions outlined above, research projects designed for a period of up to five years can be submitted. The scientific concepts and financial plans submitted should cover the same period (see 7).

A research network will receive funding for a maximum of five years. After two and a half years, the funded projects including the management programme will undergo an interim evaluation (see 7.2.2). After this interim evaluation, the network will receive further funding in accordance with the scientific recommendations of the expert panel.

When projects are being planned, particular attention should be paid to fulfilling the prerequisites for funding specified under 4 and 7.2 as well as the selection and decision-making criteria. Special attention needs to be paid to the consolidation concept.

3. Funding Recipients

German public and private universities and non-university research institutions, scientific working groups which are separate legal entities, and commercial enterprises are eligible to apply for funding. The participation of small and medium-sized enterprises (SMEs) is explicitly encouraged. The European Commission's definition of SMEs can be found online at http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm and http://ec.europa.eu/enterprise/policies/sme/files/sme_definition/sme_user_guide_de.pdf.

Research institutions that receive their basic funding jointly from the German federal government and federal states can be granted project funding for their additional expenses only under certain conditions.

4. Prerequisites for Funding

The *LiSyM Research Network* must regulate its joint efforts in a cooperation agreement. Before a funding decision can be made, proof of basic agreement on specific criteria set out by BMBF must be furnished. Details can be found in a BMBF information leaflet (<http://www.foerderportal.bund.de/> under Formularschrank – BMBF – Allgemeine Vordrucke – Vordruck 0110).

All grant recipients must acknowledge their cooperation with the programme management and the central data management. The project outline must specify the applicants' own possible contribution for setting up and organizing the research network and the willingness to exchange data within the network. Failure to submit a statement of willingness to exchange data can lead to exclusion from the further procedure.

It is a precondition 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 materials databases (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. For this purpose, the materials databases should be standardized and their previous benefits should be documented with related publications.

In their own interest, applicants should familiarize themselves with the EU Framework Programme for Research and Innovation when planning their national project. They should check whether the envisaged project has specific European components, which would make it eligible for full EU funding. Moreover, applicants should verify whether an application for supplementary funding can be submitted to the EU in the context of the planned national project. The results of this assessment should be briefly outlined in the application for national funding.

Large companies are only entitled to have their projects funded under these funding guidelines if the projects would not be implemented or not implemented to the full extent without public funding, or if public funding can accelerate development considerably, i.e. if funding provides an incentive effect under Article 8 of the General Block Exemption Regulation.

5. Type, Scope, and Amount of Funding

Funding may take the form of non-repayable grants awarded for projects. Funding for applicants not involved in commercial activities may be granted for project-related additional expenses, such as personnel costs, equipment and travel expenses. In well-justified exceptional cases, funding for these applicants may also take the form of project-related investments if they are not part of the applicant's general-purpose equipment.

Funding will be awarded for a period of up to five years. The continuation of individual research projects is subject to the result of an interim evaluation (see 7.2.2).

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), up to 100 % of which can be funded in individual cases.

The basis for calculating the grants for commercial 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 – as a general rule, at least 50 % of the total costs eligible for funding.

The European Commission's Community Framework for State Aid for Research and Development must be observed when fixing the rates for funding. This Community Framework permits differenti-

ated bonuses for small and medium-sized enterprises (SMEs), which may lead to a higher funding quota.

The relevant thresholds and rates of funding specified in the GBER will not be exceeded by the individual grants.

6. Other Terms and Conditions for Awarding Funding

The General Auxiliary Terms and Conditions for Funds Provided by BMBF to Commercial Enterprises for Research and Development Projects on a Cost Basis (NKBF98) will form an integral part of the notification of the award of cost-based grants.

The General Auxiliary Conditions for Grants for the Promotion of Projects (ANBest-P) and the Special Auxiliary Terms and Conditions for Funds provided by BMBF for the Promotion of Projects on an Expenditure Basis (BNBest-BMBF98) will form an integral part of the notification of the award of expenditure-based grants.

7. Procedure

7.1 Commissioning of a Project Management Organization and Requesting Documents

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

Project Management Jülich (PtJ-BIO)

Bioinnovation and Bioeconomy

Forschungszentrum Jülich GmbH

52425 Jülich

Germany

Tel: +49 2461 61-5543

Fax: +49 2461 61-9080

Internet: <http://www.ptj.de>

Contact:

Dr. Anne Mönning

Tel: +49 2461 61-9289

Email: a.moenning@fz-juelich.de

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

7.2 Funding Procedure

The competition for the selection of the projects to be funded consists of two stages, and includes an in-depth review involving external experts.

7.2.1 Applications

7.2.1.1 Submission and Selection of Project Outlines

In the first stage, project outlines are submitted to Project Management Jülich. The project outlines should contain all of the information needed for the panel of reviewers to make a conclusive expert recommendation on the selection of the research collaborations. In the case of young investigators groups, the project outline must be accompanied by a CV of the project leader.

The project outlines must be submitted by the early-career scientists or by the designated project coordinator after approval by all project partners.

Since an international review procedure will be carried out, it is recommended that project outlines be submitted in English.

Project outlines (descriptions of work) must be structured in the following form:

1. topic and objective of the project with a view to the goals stated under 2
2. description of own contribution to an overall strategy for establishing a *Research Network Systems Medicine of the Liver*
3. statement regarding the relevance of the selected overarching scientific issue
4. state of the art in science and technology of relevance to the project, applicants' previous work, if applicable, patent situation and economic significance
5. partners involved and their expertise
6. structure and management of the project
7. detailed description of the scientific concept including milestone planning
8. detailed financial plan including annual plans
9. strategy for data management and data standardization
10. exploitation plan
11. approaches for a consolidation concept for securing the expertise in the long term
12. need for funding

Project outlines must not exceed 25 pages (**including** appendix). Further binding requirements for project outlines are contained in the guidelines for applicants (www.ptj.de/lisym). Applications that do not meet the formal requirements may be rejected without any further consideration.

Applications must be submitted electronically via the pt(outline* portal (<https://pt-it.de/ptoutline/application/lisym>). Access via the portal is expected to be possible from late November. The project outline must be uploaded as a PDF file. Furthermore, a project overview will be generated from the data entered in the online form (data sheet). The data sheet and uploaded project

outline will be evaluated together. To ensure that the electronic version of both documents is legally valid, printed versions must be signed by the coordinator after they have been submitted electronically and sent to the responsible project management organization.

Applications may be submitted via the pt(outline* portal until 26.02.2015. The portal will be closed immediately after the deadline for submission.

The deadline for submission is not a cut-off deadline. However, it may not be possible to consider project outlines received after the specified date. For submission after the deadline, applicants must contact the responsible project management organization directly. Applications may not be submitted by email or fax.

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

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

- scientific quality of the project
- relevance to the overall concept for *Research Network Systems Medicine of the Liver*
- scientific and technical qualifications of the applicants, relevant previous work
- quality of the interdisciplinary cooperation with regard to the systems medicine approach and, if applicable, the transfer to practical applications
- quality of data management and data standardization
- project management and project structure
- quality of the exploitation plan, in particular with a view to concrete application
- information on the consolidation concept

The evaluation will form the basis for the selection of projects suitable for funding. Those involved will be informed in writing of the results of the selection process. Applicants have no legal claim regarding the return of project outlines submitted.

7.2.1.2 Submission of Formal Funding Applications and Decision-Making Process

In the second stage of the procedure, the coordinators and project leaders will receive the result of the evaluation of the project outlines together with a request to compile details of the overall strategy for the establishment and organization of the *LiSyM Research Network* in cooperation with the programme management. Clearly defined milestones for the research network as a whole must be formulated for this purpose. Furthermore, all of the partners involved must prepare their detailed working packages in the context of the overall concept.

This process is necessary in order to ensure that links are established within the *LiSyM Research Network* beyond the individual joint projects, and to facilitate efficient cooperation.

The organization of this process will be supported by the project management organization (if necessary with the support of the experts).

The selected projects/partners in the research network will also be requested to submit a formal application for funding by a set date. This will form the basis for the funding decision after a final review.

Forms for guidelines, information sheets, instructions and auxiliary terms and conditions can be accessed online at <http://www.foerderportal.bund.de/> (Formularschrank – BMBF). Copies can also be requested directly from the project management organization. Applicants are strongly advised to use the electronic application system easy-Online to prepare formal applications for funding (<http://www.kp.dlr.de/profi/easy/>).

7.2.2 Interim Evaluation

Two-and-a-half year after the start of the projects, there will be an interim evaluation of the *LiSyM Research Network*. The evaluation will focus on the results achieved by the research network, its coordination structures, and the consolidation concept with respect to the objectives listed in the announcement and the initial recommendations of the reviewers. The continuation of the individual research projects, which may require modifications to the work plan or a change of the budget for years 4 and 5, will be depended on the results of the interim evaluation.

7.3 Regulations to be followed

The 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 under § 44 of the Federal Budget Code (BHO) and §§ 48 to 49a of the Administrative Procedure Act (VwVfG) unless these funding guidelines permit an alternative procedure.

8. Entry into Force

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

Berlin, 27.10.2014

Federal Ministry
of Education and Research

Signed

Dr. Stephan Roesler