



## InnoSysTox - Moving

### INNOVATIVE SYSTEMS TOXICOLOGY FOR ALTERNATIVES TO ANIMAL TESTING – MOVING TOWARDS APPLICATION

Joint call by ZonMw, BMBF and F.R.S.-FNRS

**Deadline: 02 July 2019**

**Key words:** Replacement of animal testing, toxicology, systems biology, computational modelling

**Issued on:** 25 April 2019

#### 1. Background

Ensuring the safety of chemicals and new products requires a profound understanding of potential toxic effects of these compounds. An increasing number of legally prescribed safety tests for consumers and employees currently requires toxicity testing by using animals. Consequently, there is a continuous effort to find alternative approaches that avoid testing on animals whenever possible.

Moreover, there is a growing realization in science and society that the most appropriate model for human biology is the human. Innovative methods that are based on human biology will accelerate developments in the replacement of animal testing.

Traditional research in the life sciences has studied the properties of cell components in an attempt to understand biological phenomena. Systems biology extends such studies by employing a systemic view on biological questions. Specifically, how biological properties are determined by the interaction of the cellular components. To come to understand biological networks, mathematical models are created and used in iterative cycles of experiment, data and model evaluation, and computer simulation.

Models are abstractions that make highly complex relationships intelligible by reducing the complexity to the essential features in order to address the aim of the analysis. There are many ways of modeling, e.g. mechanistic, dynamic, statistical, mathematical, computational etc. As analytical tools, these models help to organize, explain and interpret data. They will only work on data of adequate quality, quantity, density and structure. Therefore, data and model management have become crucial components of modern life science research.

In the field of toxicology, national and international initiatives such as e:ToP, Toxicology in the 21st Century and InnoSysTox are seeking to bring about a mind shift towards human biology. This will enable more information to be derived from *in vitro* or *in silico* tests and thereby reduce the use of *in vivo* (animal) studies. This aim can be realized by modelling toxicological pathways and inclusion of kinetic and dynamic data as well as by data analysis, visualization and integration, for example. Establishing these integrated toxicological testing strategies ultimately fosters a more specific

prediction and quantification of human health risks and, at the same time, an enormous reduction of animals used in experiments.

In order to combine resources and infrastructures, and to consolidate and strengthen international collaboration in the development of 3R research, systems biology, bioinformatics and toxicology, ZonMw and BMBF organised a first joint call for transnational, multidisciplinary projects in 2014.

To further strengthen the field in Europe and to foster and consolidate sustainable research cooperation of Germany, the Netherlands and Belgium, a follow-up joint call for interdisciplinary research projects is being launched by ZonMw (Netherlands Organization for Health Research and Development), BMBF (German Federal Ministry of Education and Research) and F.R.S.-FNRS (Fund for Scientific Research-FNRS).

## **2. Objectives and Considerations for the Call**

### **Main Objectives**

*Development and Application* of innovative systems-biology-based Replacement methods in toxicology

### **Considerations**

- *Contribution to Replacement:* the joint project proposal must set out arguments for the impact of the project on the replacement of animal testing by alternative methods or models. A concrete, existing animal method or model has to be addressed and the impact on replacement of this animal experiment has to be described clearly in the application. In this call, projects are not allowed to initiate or perform animal testing.
- *Application of research results:* joint projects have to contribute to a concrete, targeted and timely transfer of results and data into broad application. Existing alternative toxicological test approaches are to be significantly further developed and prepared for a timely and broad implementation into applied sciences. Technology Readiness Levels (TRL) 2-4 must be addressed in the collaborative project (see below). See National Annex for specific regulation.
- *Interdisciplinarity and Transdisciplinarity:* each joint project must embrace systems biology, toxicology and Replacement of animal testing. The project should deliver added value through international collaboration in a consortium of public and private partners. Visits and internships among consortium partners are strongly encouraged.
- *Public-Private Partnership:* the joint project must be based on an international public-private partnership in a broad-based strategic consortium.
  - o Each project consortium must have at least three partners: two public partners and one private partner.
  - o A private partner may be any international company. Please note that there are differences in national criteria concerning the eligibility of private partners for funding. Please read the National Annexes!
  - o Each consortium must contain partners eligible for funding by at least two funding organisations participating in this call (ZonMw, BMBF and F.R.S.-FNRS).
  - o Participants from countries outside Germany, the Netherlands and Belgium may be involved in a project if they secure their own funding and if their expertise is indispensable to achieving the project objectives. Private participants from these countries can contribute the required matched funding (see definition below).
- *Mathematical Modelling:* Mathematical modelling and computer simulation with experimental validation of model predictions have to be implemented in the project. As an integral part,

modeling should commence from the beginning of the project. Computational models based on relevant, high-quality datasets (sufficient deep phenotyping, curated data sets) should already exist. Well annotated archived samples should be available. New data may only be generated when it is necessary for the modeling cycle, therefore generation of new data cannot be a major part of the project.

- *Data and Model Management:* A data management plan and data handling protocols according to internationally state-of-the-art standards (FAIR<sup>1</sup> and GDPR<sup>2</sup> compliant and secure) must be provided as an integral part of the application. A data management plan should address criteria such as data accessibility, format and storage, stewardship/curation, time plan and schedule for the submission date, quality of meta data, and data security. For this, it may help to refer the Horizon 2020 data management plan (DMP) template [[http://ec.europa.eu/research/participants/data/ref/h2020/other/gm/reporting/h2020-tpl-0a-data-mgt-plan-annotated\\_en.pdf](http://ec.europa.eu/research/participants/data/ref/h2020/other/gm/reporting/h2020-tpl-0a-data-mgt-plan-annotated_en.pdf)]. A reliable concept concerning data storage, data/model exchange and data/model sharing should be available at the time of application and be part of the consortium agreement (see below). The use of existing infrastructure (e.g. ELIXIR<sup>3</sup>) should be taken into consideration.
- *Regulatory Involvement:* regulators (national and/or international) must be consulted as advisors from the outset of the joint project. The project proposal must set out how this is to be arranged.
- *Implementation Plan:* the proposal must contain a plan for concrete, timely and broad implementation of research results. Identification of stakeholders should also be part of this plan.
- *Consortium Agreement:* within six months of the grant being awarded, the consortium partners must sign an agreement specifying, among other things, the approach to intellectual property rights (including data and models) derived from the results of the joint project. The consortium agreement should therefore include a set of rules and procedures to ensure fair protection for the IPR interests of the partners and their employees. The consortium agreement should also include conflict resolution procedures and mechanisms which can be invoked if and when necessary.

Applicants are strongly advised to read the National Annexes for further specifications regarding the call.

### 3. Definitions used in this Call

#### *Systems Biology*

Systems biology is a scientific approach in life sciences which aims to reach an integral and comprehensive understanding of the quantitative behaviour of biological systems that arises from the dynamic interplay of the various components thereof. As a basic prerequisite, systems biology research projects integrate mathematical models that simulate *in silico* the system's properties and predict its quantitative response to internal or external perturbations. Frequently, biological systems are represented as networks of interacting elements in which the phenotypic traits are determined by the structure and the dynamic behaviour of the network itself. The study of biological systems in this

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<sup>1</sup> Findable, Accessible, Interoperable, Reusable

<sup>2</sup> General Data Protection Regulation

<sup>3</sup> European life-sciences Infrastructure for biological Information

framework requires interdisciplinary cooperation and a division of labour between e.g., biologists, medical scientists, mathematicians, physicists, computer scientists, chemists and engineers. In systems biology, the biological questions are addressed by integrating experiments in iterative cycles with the aid of computational mechanistic modelling, simulation and predictive theory. Modelling is not the ultimate goal, but rather a tool to increase the understanding of the processes of biological systems, to develop more pertinent experiments, and finally to allow predictions. Existing and/or newly generated datasets are used to develop mathematical models of biological processes. Simulations from these models provide input for experiments in the wet lab, leading to new and better datasets. Repetition of this cycle will increase the knowledge of biological processes.

#### *Phase of Research*

The European Union defines three phases of research according to the state aid rules

[\[https://ec.europa.eu/regional\\_policy/sources/docgener/guidelines/2017/application\\_of\\_state\\_aid\\_rules.pdf\]](https://ec.europa.eu/regional_policy/sources/docgener/guidelines/2017/application_of_state_aid_rules.pdf):

- *Fundamental research* is geared at gaining new knowledge of the fundamental aspects of apparitions and perceptible facts without aiming at direct commercial application or direct commercial use.
- *Industrial research* is geared at gaining new knowledge and skills aiming for the development of new products, methods or services, or the improvement of existing products, methods or services.
- *Experimental development* is geared at the use of existing scientific, technological, business or other relevant knowledge and skills aiming at the development of new or products, methods or services.

Another well-known definition of phase of research is the Technology Readiness Level (TRL)

[\[http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga\\_en.pdf\]](http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga_en.pdf):

- TRL1: Basic principles observed
- TRL2: Technology concept formulated
- TRL3: Experimental proof of concept
- TRL4: Technology validation in laboratory
- TRL5: Technology validation in relevant environment
- TRL6: Demonstration in relevant environment
- TRL7: Demonstration in operational environment
- TRL8: System complete and qualified
- TRL9: Successful mission operations

Fundamental research comprises TRL1. Industrial research comprises TRL2-4. Experimental development comprises TRL5-8.

#### *Public-Private Partnership*

A long-term arrangement, whereby one or more research institutes collaborate(s) on a joint project with one or more private partners, in which each party retains its own identity and responsibility, and works on the basis of a clear and appropriate allocation of tasks and risks.

## **4. Conditions**

### **4.1 Project duration**

Each joint project consortium may apply for a joint project time scale of a maximum of four years. German project-related personal costs can be funded for a total of up to 36 person-months.

## **4.2 Public-Private Research Projects**

This call for public-private research projects is designed to bring about the development and application of Replacement of animal testing in systems toxicology. A public-private partnership may consist of a consortium of several public and private partners. A public partner will supply the project leader (also the main applicant), who will liaise with ZonMw, BMBF and F.R.S.-FNRS throughout the procedure. All the other partners (public and private) are co-applicants. The call is open to co-applicants from any international company.

## **4.3 Who is eligible to apply?**

Specific regulations are provided in National Annexes (8.0 Downloads).

## **4.4 Available Funding**

A total budget of about M€ 3.8 is expected to be available for the call. The contributed budget of the individual funding organizations is allocated to the respective national research groups. National funding regulations are provided in the National Annex of each funder (8.0 Downloads).

### *Matched funding*

In accordance with the Dutch LSH Topsector requirements, in all consortia that include a Dutch partner (public and/or private) the private partner(s) must provide matched in-kind or in-cash funding of 10% of the total project budget. Please refer to national funding regulations.

## **4.5 Policy on Intellectual Property**

Each consortium must agree on a consortium agreement (CA), which must be signed by all public and private partners in the joint project within six months of the grant being awarded. The consortium agreement must specify the intellectual property policy of the consortium, which should include the arrangements for ownership rights to intellectual property in the form of knowledge, products etc. developed during the project.

In this call ZonMw, BMBF and F.R.S.-FNRS have based their intellectual property policy on the principle of 'ownership follows inventorship'. In compliance with the EC Framework for State Aid for Research and Development and Innovation (2006/C 323/01),<sup>4</sup> specifically Article 3.2.2 'Collaboration of undertakings and research organizations', the intellectual property agreements must guarantee that:

- the results of joint projects from which intellectual property rights may be derived may be widely disseminated, and any intellectual property rights ensuing from the activities of the public partner(s) are awarded in full to the public partner(s).
- the public partner(s) receive remuneration from the private partner(s) in accordance with the market price for any intellectual property rights ensuing from the joint project that are transferred to the private partner(s). Any contribution by the private partner(s) to the costs incurred by the public partner(s) will be deducted from the remuneration.

Consortia are strongly advised to contribute publications and information on data, tools and technologies generated by their research to the public domain where it should be made widely available. Access must be provided to other bona fide research groups, with the necessary arrangements in place.

It is the responsibility of each project partner to ensure that intellectual property rights ensuing from the accomplishment of the joint research projects are efficiently and properly protected and distributed.

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<sup>4</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:323:0001:0026:en:PDF>

## 5. Assessment Procedure

Grants will be awarded on the basis of an assessment of the joint proposal.

### 5.1 Procedural Criteria

Applicants are required to submit one joint transnational proposal. With regard to the international review process, joint project proposals should be written in English.

The consortium leader must submit the following attachments:

- The full application form which includes an itemized budget and specifications of the matched funding by the private partner(s) in kind or in cash;
- Biosketch, to allow better assessment of the expertise of the project leader and research group. No more than two single-sided A4s per person. A document format is available (see 8.0 Downloads);
- A letter of commitment from each private partner confirming that they will join the project consortium and contribute to the proposed research, and specifying their share in the budget.

Applicants may also include an optional attachment of no more than two A4s containing figures and tables. No other attachments will be considered in the assessment of the application.

In the event that a grant is awarded, joint project coordinators are expected to:

- submit a progress report (mid-term) and a final report summarizing the achievements of the project (templates will be made available) according to national funding regulations;
- attend Status Seminars (provisionally planned at the middle and end of the project) and present the project results;
- ensure that the hours worked by staff supplied by third parties are registered.

### 5.2 Proposal Evaluation

All proposals will be subject to peer-review of the funding organisations participating in the call.

Ineligible proposals will be rejected and cannot be re-submitted. Eligible proposals will be forwarded to external, international reviewers specialized in the respective fields. These remote experts will assess the proposal and provide a standardized written evaluation. Based on the remote evaluations, proposal coordinators will be invited to submit a rebuttal. Submission of a rebuttal letter will be on a voluntary basis.

A selection of the external, international experts solicited to evaluate the proposals will be invited to form a Peer Review Panel (PRP) encompassing the necessary expertise to cover the call theme in experimental and computational research and include members with expertise in the field of basic and applied sciences, policy and development. External experts / PRP members will not participate in decisions in which they have conflicts of interest. PRP-members will be asked to be present at Status Seminars (mid-term meeting and final meeting).

Proposals will be assessed by the PRP, taking into account the remote evaluations and the candidates' rebuttal. A physical PRP meeting will be organised in which all proposals will be discussed and a consensus grade will be attributed to each proposals based on the discussions. The PRP will establish a ranking list of high-quality and relevant applications recommended for funding.

The final selection of projects to be funded will be based on a decision process of the funding organisations participating in the call.

JCS will communicate the results and findings to the applicants.

### **5.3 Assessment Criteria**

Each joint proposal will be assessed for relevance and quality.

#### *Relevance*

- The joint proposal should be consistent with the main objectives of the call set out in Chapter 2
- The joint proposal must set out arguments for the impact of the project on Replacement of animal testing
- The interdisciplinary and transdisciplinary nature of the proposal must contribute to the main objectives of the call
- The international public-private partnership in a broad-based strategic consortium must be of added value to the objectives of the call

#### *Quality*

Joint proposals will be assessed on the basis of:

- the innovative nature, clarity and scientific quality of the proposed research:
  - o originality and innovative nature
  - o scientific quality
  - o clarity of the research question and the concrete animal experiment addressed for replacement
  - o effectiveness of the implementation of mathematical modelling and computer simulation with experimental validation of model predictions
  - o effectiveness of the data management plan in addressing criteria such as data accessibility, format and storage, stewardship/curation, time plan and schedule for the submission date, quality of meta data, and data security
- the suitability of the action plan:
  - o feasibility of the project and completion of the proposed research within the planned timescale
  - o concrete step-by-step plan, including task allocation, milestones and deliverables
  - o effectiveness of the chosen approach
  - o effectiveness of the data management
  - o effectiveness of communication and implementation of the results, both during and after the project (including regulatory involvement)
  - o soundness of the budget
- the academic standard and expertise of the project consortium:
  - o academic excellence and international competitiveness, demonstrated by academic publications, awarded grants and prizes, networking, training, mobility and supervision of staff
  - o added value through international collaboration
  - o complementarities and balance
  - o experience of inter- and transdisciplinary research

Each joint proposal is assessed for relevance and quality. The evaluation committee will rank the proposal using the matrix below, where applications will be ranked in categories from A (highest) to D (lowest). A joint proposal must achieve at least 'relevant' and 'very good' to be eligible for funding.

		RELEVANCE		
		Very relevant	Relevant	Not relevant
QUALITY	Excellent	Category A	Category C	-
	Very Good	Category B	Category D	-
	Good	-	-	-
	Sufficient	-	-	-
	Unsatisfactory	-	-	-

## 6. Contact

### National Contact Points

Applicants are encouraged to contact their respective National Contact Point for any queries related to contend or national regulations:

#### *ZonMw - The Netherlands*

Dr. Rob Diemel, programme officer, tel. +31 (0)70 349 5252, email: [diemel@zonmw.nl](mailto:diemel@zonmw.nl)

Dr. Erica van Oort, programme officer, tel. +31 (0)70 349 5326, email: [e.oort@zonmw.nl](mailto:e.oort@zonmw.nl)

#### *BMBF / PtJ - Germany*

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

Projektraeger Juelich (PtJ), Lebenswissenschaften und Gesundheitsforschung (LGF) -BioMedizin (LGF 3)-, Forschungszentrum Juelich GmbH, 52425 Jülich, Germany.

Dr. Sonja Matthiesen, tel. +49 (0)2461 61-96455, email: [s.matthiesen@fz-juelich.de](mailto:s.matthiesen@fz-juelich.de)

Dr. Rudi Loesel, tel. +49 (0)2461 61-96451, email: [r.loesel@fz-juelich.de](mailto:r.loesel@fz-juelich.de).

#### *F.R.S.-FNRS - Belgium*

Florence Quist, Ph.D., Conseillère Scientifique/Scientific Officer European and International Affairs, tel: +32 (0)2 504 93 51, email: [florence.quist@frs-fnrs.be](mailto:florence.quist@frs-fnrs.be).

### Joint Call Secretariat

For questions on the application procedure, please contact the Joint Call Secretariat:

Projektraeger Juelich (PtJ), Lebenswissenschaften und Gesundheitsforschung (LGF) -BioMedizin (LGF 3)-, Forschungszentrum Juelich GmbH, 52425 Jülich, Germany.

Dr. Sonja Matthiesen, tel. +49 (0)2461 61-96455, email: [s.matthiesen@fz-juelich.de](mailto:s.matthiesen@fz-juelich.de)

Dr. Rudi Loesel, tel. +49 (0)2461 61-96451, email: [r.loesel@fz-juelich.de](mailto:r.loesel@fz-juelich.de).

## 7. Submission of Proposals via Online Submission Tool

One joint proposal document shall be prepared by the partners of a joint transnational consortium and submitted electronically by the coordinator via the online submission tool (<http://innosystox-moving.ptj.de>). Only proposals using the template available in the submission tool (also see 8.0 Downloads) will be accepted. No other means of submission will be accepted.

The submission deadline for proposals is no later than **July 02<sup>nd</sup>, 2019**.

Detailed Information on how to submit joint proposals, required documents and other binding requirements for the project proposal can be found in the online submission tool (<http://innosystox-moving.ptj.de>).

## **8. Downloads**

The required documents can be found in the online submission tool (<http://innosystox-moving.ptj.de>) under call documents.

- Biosketch format
- Letter of commitment

### **8.1 ZonMw specific Documents (ZonMw applicants)**

- Dutch National Annex

### **8.2 BMBF specific Documents (BMBF applicants)**

- Richtlinien zur Förderung zur transnationalen Förderinitiative "InnoSysTox – Innovative Systemtoxikologie als Alternative zum Tierversuch – Hin zur Anwendung"
- For eligible costs and further national regulations please refer to national guidelines applicable to applications to BMBF: <https://foerderportal.bund.de/>
- Merkblatt für Antragsteller/Zuwendungsempfänger zur Zusammenarbeit der Partner von Verbundprojekten, BMBF-Vordr. 0110/08.14

### **8.3 F.R.S.-FNRS specific Documents (FNRS applicants)**

- National Annex French speaking community in Belgium