iBOS

integration of biosynthesis and organic synthesis

Call for proposals

Fourth tender for SME projects for the NWO-ACTS programme IBOS: Integration of Biosynthesis and Organic Synthesis

NWO
Netherlands Organisation for Scientific Research

Ministry of Economic Affairs

ACTS

The Hague, November 2008

Contents

1 Introduction

This Programme Outline & Call for proposals briefly describes the scope and intentions of the ACTS Research Programme IBOS (Integration of Biosynthesis & Organic Synthesis), and gives detailed information on the conditions for research proposals within the framework of this Programme. Furthermore, a time schedule for the funding process is provided.

All necessary documents are also accessible via the IBOS website: www.nwo.nl/ibos.

1.1 ACTS

The IBOS Programme is financed and its effective execution stimulated through *ACTS* (*Advanced Chemical Technologies for Sustainability)*. ACTS is the Dutch platform for pre-competitive research in the field of catalysis, with major parties from industry, academia and government as stakeholders. As its Mission it states: *ACTS establishes pre-competitive, scientifically ambitious research Programmes in areas where catalysis plays a pivotal role, as identified by the 'Technology Roadmap Catalysis'. ACTS embodies the aspiration of these partners to initiate and support the development of new technological concepts for the sustainable production of materials and energy carriers, particularly those which are essential for the supply of food, comfort, health, shelter and mobility, for the inhabitants of tomorrow's world. Through its activities ACTS contributes to the sustainable economic growth, to the knowledge infrastructure in the Netherlands and to the attraction of young talent to a career in science and technology.* ACTS is part of the Dutch Research Council (NWO). More information on ACTS can be found on www.nwo.nl/acts

1.2 IBOS programme

The ACTS IBOS Programme is a M€ 13.6 research programme financially supported by the Dutch chemical and life sciences industry (including SMEs), the Dutch ministry of Economic Affairs and the Netherlands Organisation for Scientific Research (NWO).
The programme is open to all tenure (track) researchers of Dutch universities and other Dutch predominantly academic institutes.

As a result of the success of the first, second and third Call for Proposals SME projects, the IBOS Programme Committee continues to foster innovation-oriented research cooperation between academia and SME (MKB: Midden en Klein Bedrijf) companies[1]. The rules are kept the same as in the former calls. Research subsidies can be applied for short (one or two year) postdoctoral projects. An SME contributes one third of the total project budget, with the possibility to supply this contribution largely *in kind*. A minimal cash contribution by an SME of around k€ 10 or k€ 20 for one or two year-projects, respectively, is required.

The current tender forms the fourth tender for SME projects, which will be the last tender in the IBOS programme. The fourth call has a budget of approximately k€ 650.

[1] In the *Regeling in kind bijdragen door MKB in IBOS* (only available in Dutch), SMEs are defined and rules for participation are described (www.nwo.nl/ibos).

2 Aim

IBOS focuses on new dimensions for both organic synthesis and biosynthesis:

- Development of multifunctional catalytic methods in (bio)organic synthesis (making a number of bonds simultaneously);
- The end of protective group chemistry, elaborate purifications and waste;
- Onepot cascade syntheses;
- Development of devices for bio-organic processes (bioprocess engineering)
- Cell factories for the production of natural and non-natural products (e.g. for health, food);
- Shorter time-to-market by modular process steps (e.g. processes on chips/ microreactors).

Research in the programme is oriented along four research lines:

- Molecular Biology & Biosynthesis;
- Bio-transformations;
- Bio-inspired Organic Synthesis;
- Bioprocess engineering.

For a more extensive description, please view the original programme outline (see section 6).

The proposal should fit within the IBOS research lines described above. The character of the research should be innovative, oriented towards the development of an application.

3 Guidelines for applicants

3.1 Who can apply?

An academic research group applies for the project. The SME acts as the industrial partner, and, especially in case of an *in kind* contribution, participates actively in the project. It is formally not considered as an applicant[2].
A clear description of the involvement of the SME in the proposed research is necessary.

Professors, associate professors and assistant professors as well as other researchers can apply if they:
- are employed at a Dutch University or a research institute recognised by NWO or at a GTI (TNO, ECN, A&F)[3] and
- have an employment contract for at least the award period of the grant.

3.2 What can be applied for?

- **Personnel**. Budget for postdoctoral researchers may be requested:
  Postdoc/researcher (1 year): ~k€ 63[4]
  Postdoc/researcher (2 years): ~k€ 127[4]
  Man hours of SME labour costs[5]

Workplans for all researchers, including SME researchers, must be provided.

- **Consumables**. Expenses for consumables can be budgeted to a maximum of k€ 12 (including VAT/BTW) per year per researcher or technician.

- **Equipment**. Only special and dedicated equipment that directly relates to the proposed research may be applied for. Motivation and specification is necessary and will be evaluated. Use of special SME equipment (*in kind*) is to be judged by the IBOS Programme Committee.

3.3 When can applications be submitted?

The deadline for submission of the proposals is 12 March 2009 (23.59 hrs). Proposals should be received no later than this deadline. Proposals can not be altered or supplemented after the deadline.

3.4 Drawing up an application

- Proposals must comply with the rules stated in this brochure and must be submitted in the prescribed format;

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[2] See the *Regeling subsidieverlening door ACTS* (only available in Dutch), which can be downloaded from the ACTS website (www.nwo.nl/ibos)

[3] Researchers working at the GTI´s (TNO, ECN, A&F) can apply according to the arrangement for GTI´s as approved by the Executive Board of ACTS.

[4] Tariffs as of 1 July 2008. The VSNU tariff for a postdoc includes a personal fee for congress travel and fees (bench fee)

[5] See *Regeling in kind bijdragen door MKB in IBOS* (only available in Dutch, www.nwo.nl/ibos)

- The application form and the guidelines for the form can be downloaded from the IBOS website: www.nwo.nl/ibos.

3.5 Specific conditions

3.5.1 Eligible in kind SME costs

A budget application should contain a 1- or 2-year (postdoctoral) researcher at an academic research institute. Materials (bench fee, max. k€ 12 per year) and other expenses can be added. If the application contains in kind contributions by the involved SME, these should be part of the application.

SME in kind costs may comprise:
- man hours (see paragraph 3.2)
- (use of) equipment
- materials, enzymes, cultures, etc.

Supervising costs or programme management costs are not eligible!

All in kind costs must be accounted for to ACTS (audit). Only when the total committed in kind contribution by SME's is accounted for, subsidies can be made definitive. For the exact rules concerning in kind contributions see the *Regeling in kind bijdragen door MKB in IBOS* (only available in Dutch) (www.nwo.nl/ibos).

3.5.2 Overhead costs

ACTS is a funding organisation that executes IBOS and other programs with money supplied by third parties, of which the industry is one. Overhead costs are included in the programme budgets (5%). On top of that, IBOS has a budget for "network costs" (2%) for organising conferences and communication of research results. All partner contributions, including the industrial contribution to IBOS projects, are therefore increased with 7%, which is also reflected in the examples under paragraph 3.5.4.

3.5.3 Intellectual Property Rights

The rules for Intellectual Property Rights are derived from the ACTS Covenant (2002) between the government, industry and academia, which says that:

All knowledge and know how resulting from an ACTS programme or project is the joint property of the organizations participating in that programme or project. When this knowledge or know how concerns a commercially exploitable invention, its first publication will be in the form of a patent application. The involved industrial partners have the right of first refusal. In the first instance the right to file a patent application is for one or more of the (industrial) partners in the project/programme against a market-conform reimbursement, which includes in any case the projects costs.
Publication of results and inventions in the public domain has a high priority; it can only be delayed by a reasonable term for filing a patent application.
An agreement between ACTS and the SME will be made describing specific rules and conditions for obtaining IP or using know how.

The text of the ACTS Covenant can be requested at the ACTS office (for contact information, see section 5). Check IPR-regulations with your SME-partner before submitting your proposal to ACTS.

3.5.4 Examples for budgets

Example 1

Budget		**Contributions by**	
1-year postdoctoral researcher	k€ 63	NWO/Government (two third part)	k€ 63
Total material costs	k€ 25		
Bench fee	(k€ 12)	SME (one third part of total)	k€ 31
Equipment (use/purchase), or enzymes, cultures etc.	(k€ 13)	(k€ 12.5 *in cash* / k€ 18.5 *in kind*)	
Total project budget	k€ 88		
Overhead costs and networking[6]	k€ 6		
Total expenses	k€ 94	Total contributions	k€ 94

In this example, the SME contributes k€ 10.5 cash to the project and k€ 18.5 *in kind* (material costs only), and k€ 2 (*cash)* to overhead and networking costs.

Example 2

This example reflects the intended cooperation better, as also man hours of the SME are included in the project:

Budget		**Contributions by**	
1-year postdoctoral researcher	k€ 63	NWO/Government (two third part)	k€ 76
Employee SME 1 day/week, 1 yr	k€ 20		
Total material costs	k€ 23		
Bench fee	(k€ 12)	SME (one third part of total)	k€ 37.5
Equipment (use/purchase), or enzymes, cultures etc.	(k€ 11)	(k€ 15 *in cash*[7] / k€ 22.5 *in kind*)	
Total project budget	k€ 106		
Overhead costs and networking[7]	k€ 7.5		
Total expenses	k€ 113.5	Total contributions	k€ 113.5

In this example the SME contributes k€ 12.5 cash to the project, k€ 22 *in kind* (man hours (k€ 20) and material costs (k€ 2)) and k€ 2.5 (*cash)* to the overhead costs.

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[6] 7% of the applied project budget is added (cash!) for overhead costs and networking. Round numbers were used. Note: the total required cash commitment of the SME is 1/3 × 1/3 of the total expenses + 1/3 of the overhead costs and networking. In the example above: k€ 10.5 + k€ 2 = k€ 12.5 minimal cash contribution.

[7] 7% of the applied project budget is added (in cash!) for overhead costs and networking. Note: the total required cash commitment is 1/3 × 1/3 of the total expenses + 1/3 of the overhead costs and networking. In the example above: k€ 12.5 + k€ 2,5 = k€ 15 minimal cash contribution.

3.6 Submitting an application

- Applications should be submitted 12 March 2009 (23.59 hrs.) at the latest via the NWO Iris electronic system, to be reached via www.nwo.nl/ibos. The IBOS Application Form Fourth Call for SME Projects 2008 must be used and can be downloaded via www.nwo.nl/ibos.
- In accordance with the agreement between NWO and the Association of Dutch Universities (VSNU), applicants should inform their employing institute of the submission. You should send a copy of your application to the scientific director or dean of your institute of department. If you submit a proposal, ACTS will assume that you have informed your university or institute and that it accepts the granting conditions of this programme.

4 Assessment procedure

4.1 Procedure

The IBOS Programme Committee will evaluate the proposals according to the criteria (see paragraph 4.2) and advise the Executive Board of ACTS about the granting (April 2009).

4.1.1 Final decision

The Executive Board of ACTS will take the final decision about which proposals to grant, based upon the ranking and funding recommendations from the Programme Committee.

4.1.2 Time-Table

12 March 2009	**deadline submission proposals**
March 2009	PC ranks the proposals
April 2009	funding decision by ACTS Executive Board
May 2009	applicants are notified about funding decisions

4.2 Criteria

The criteria on which the proposals will be evaluated are:
- Participation (in kind and/or in cash only) of one (or more) SME(s);
- Their compliance with the IBOS programme;
- Innovativeness and quality;
- Aims, deliverables and timeline of the proposed research;
- Budget applied for in relation to the proposed research.

4.3 Composition of Programme Committee

As appointed by ACTS, IBOS has its own programme committee, consisting of senior representatives from academia and industry. The present members of this committee are:
- Dr. M. Schreuder Goedheijt (Schering-Plough) (chairman)
- Prof. dr. ir. J.J. Heijnen (Delft University of Technology) (vice chairman)
- Dr. Q.B. Broxterman (DSM)
- Prof. dr. A.J.M. Driessen (University of Groningen)
- Dr. W. Duetz (Enzyscreen)
- Prof. dr. R.M. Kellogg (Syncom)
- Prof. dr. F.P.J.T. Rutjes (Radboud University Nijmegen)

M. Schmets, MSc. (ACTS, *programme manager*) ibos@nwo.nl

5 Other information

5.1 Contact information

For more information please contact the IBOS Programme Manager:

- M. Schmets, MSc.
- Advanced Chemical Technologies for Sustainability (ACTS)
  Netherlands Organisation for Scientific Research (NWO)
- 51, Anna van Saksenlaan
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- E-mail: ibos@nwo.nl
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or contact members of the programme committee (see paragraph 4.3; contact details available upon request).

6 Programme Outline

IBOS focuses along four research lines:

A. Molecular Biology & Biosynthesis
B. Bio-transformations
C. Bio-inspired Organic Synthesis
D. Bioprocess engineering

A. Molecular Biology & Biosynthesis

Fundamental knowledge about biological systems has increased enormously in the last 25 years. At molecular level the actions of enzymes and metabolic pathways can now be identified. To translate this know-how into new bio-syntheses and bio-catalysts, additional insight is needed in the operation of complete microorganisms, individual cells, cell compartments, enzyme interactions and metabolic fluxes. Challenging are in particular the further studies of the role of compartments in cells and of the mechanisms of the several process-couplings involved. The control of enzyme levels and activation between genome and proteome and the associated molecular recognition systems need to be understood in detail. In order to widen the scope of fermentation processes interactions between primary and secondary metabolisms should be elucidated. Transport-mechanisms into, within and out of a cell or cell compartment should be known as well for natural products as for (new or known) non-natural molecules. In particular transport-proteins and mechanisms involved in product removal should be understood in much greater detail. New or revised systems might be needed to allow high throughputs.
Genetically engineered bio-systems should be made available to improve biosyntheses of both enzymes for biocatalyst development and metabolic end products (natural and non-natural). In particular fermentation of non-natural molecules will need full deployment of all available tools in molecular biology. Further exploitation of directed evolution methods will greatly enhance this (including developments, in genomics, biomolecular informatics etc.)

B. Bio-transformations

Although the present approach of using one enzyme for a particular conversion can still be widened in scope the challenge should be at employing combinations of enzymes.
Cascades of enzymatic reactions are already emerging but can be researched much wider. Biocatalysts consisting of a number of enzymes acting in concert and inter-dependent such as in redox reactions should be made available. More simple and cheaper co-factor regenerating systems should be developed and built into a biocatalyst. The present focus on single enzyme biocatalysts should further be shifted to enzyme combinations, cell compartments or even complete cells as catalyst whereby several enzymes are indeed employed. Nowadays whole cell systems are already used as biocatalyst but mainly employing only one of the enzymes present. Often these enzymes cannot be isolated and/or are deactivated upon isolation. Further challenges are new techniques for formulation of enzymes and enzyme systems into stable, robust and efficient biocatalysts.
Single bio-catalytic conversions and biotransformations using enzyme combinations should become a synthetic continuum with precursor fermentations and direct fermentations. Insight in interaction of enzymes with their environment (i.e.

membranes) will hereby be needed. Methods to tune enzyme kinetics will be required. Artificial co-factor regenerating systems will have to be developed as well as new in-situ-product-removal (ISPR) methods.

C. Bio-inspired Organic Synthesis

Many organic syntheses are already inspired by nature. However, the complexity of biology has forced organic chemistry to very inaccurate translations of enzyme systems into man-made catalysts (i.e. catalysts with a simple molecular structure and mol. weight below 500 vs. enzymes with highly intricate structures and mol. weights up to 500.000).
The present bio-inspired trend in organic synthesis towards macromolecular systems is meeting the advancement in molecular biology at the same level. This should lead to joint design of new multifunctional (bio-)catalyst systems, which can either be used in a modified metabolic path for a fermentation process or as an efficient catalyst in a series of organic syntheses.
Bio-mimetic catalyst systems will be made available designed on growing knowledge of metabolic pathways and detailed insight in bio-recognition phenomena.
Biomolecular informatics will provide guidelines for the design of new and robust catalysts. When combined with mechanistic know-how of chemo-catalysis ‘de novo’ enzyme design comes within the realm of current chemistry. Combination with directed evolution methods would be another way to new catalyst design. High selectivity for a specific target molecule can be reached.
Better bio-, chemo- and hybrid-catalyst formulations for a wide range of (bio) syntheses will be the result utilizing enzymes, metals and a range of dedicated ligands. Increased knowledge of active site structures, effect of protein modifications, functional insight in enzyme systems, cell compartments and even complete cells will be at the basis of these new developments together with the mechanistic insights from chemo-catalysis.

Specific challenges in synthetic organic chemistry are:

- Direct functionalization of aromatic compounds (for instance replacing Friedel Crafts type);
- Chemistry by direct arene alkylation/acylation using olefins;
- Cross coupling reactions, which play a prominent role in current synthetic repertoire, based on olefins;
- (Bio-)catalytic reductions and oxidations;
- Synthetic conversions without protective groups;
- Catalytic methodology in heterocyclic chemistry. Numerous bioactive products in particular pharmaceuticals and agrochemicals are based on multifunctional heterocyclic compounds. Hardly any of the current catalytic methods can be employed for heterocyclic substrates due to rapid catalyst poisoning.

Another major challenge is the reduction of the number of steps in common multistep synthesis. The combination of mutually depending bio- and chemo-catalysis is only one of the possibilities to develop synthetic methods not depending on exhaustive protective group manipulation.
Eventually multi-step, once-through processes will evolve from exceptions today to common methodology tomorrow. Combining “combinatorial approaches” with “understand, design and build”-methods will be an additional challenge in reaching these new synthesis methodologies.

D. Bioprocess Engineering

Bioprocess Engineering deals with the design and development of equipment and processes for the manufacturing of products such as food, feed, pharmaceuticals, nutraceuticals, chemicals, and polymers and paper using biocatalysts, micro organisms and cell cultures.
Application areas commonly associated with bioprocess engineering include the production of biofuels, design and operation of fermentation systems, development of food processing systems, application and testing of product separation technologies, design of instrumentation to monitor and control biological processes, and many more. Like other engineering disciplines, bioprocess engineers are trained in the application of engineering sciences and problem solving techniques. What separates them from other engineers is their understanding of living materials.

Specific challenges in Bioprocess Engineering:

- Proposals should propose new bioprocess (reactor + down stream processing) concepts, e.g. micro-reactors, single use fermentors, integration with respect to in situ product removal or other.
- Use of such new bioprocess concepts for High Through put screening of biocatalysts / micro organisms / cell cultures and/or scaled up production of a new product.