CTMM 2008 CALL FOR PROPOSALS

The Second Call for proposals for the CTMM initiative opens in October 2008. The deadline for submitting proposals for CTMM 2009 is Sunday, November 30, 2008 at 24:00 h.

The Center for Translational Molecular Medicine (CTMM) is a public-private partnership which aims to become the leading Netherlands-based innovator of Molecular Diagnostics and Molecular Imaging technologies which enable the advancement of Molecular Medicine.

CTMM is funding translational research, up to and including preclinical and early clinical proof-of-concept research that transitions technologies from exploration to validation and from the laboratory to the patient. CTMM aims to deliver technologies that have a clear and proven clinical relevance, contribute to the containment of the increasing cost of healthcare, form a substantial contribution to the scientific community and have potential commercial value. The CTMM research framework supports the translational approach by defining research programs by disease area or by technology platform(s) from exploration to clinical validation. CTMM projects are performed by academia and industry in close cooperation.

The call for proposals' scope

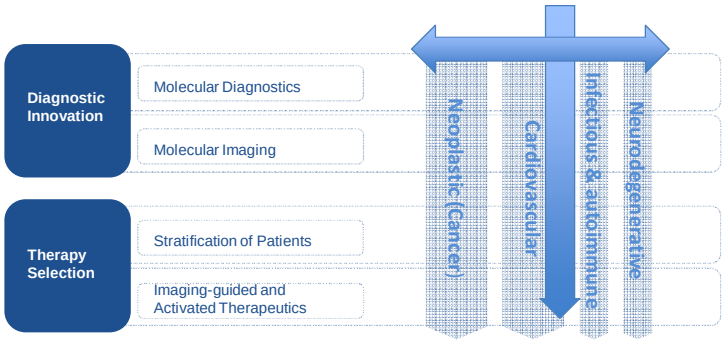
CTMM invites consortia of academia, research institutes and industry to submit proposals for research projects that fit within the call objectives and do not show substantial overlap with approved proposals from the first call. The overall objectives of CTMM can be categorized in three directions, viz. to perform top quality research, to generate economic value and to create clinical value. Given the fact that the CTMM program will be composed of a comprehensive set of different projects, project proposals are expected to address their contribution to the overall program objectives in sufficient detail, both qualitatively and quantitatively, to enable adequate review and ranking.

The overall ambition of CTMM, as expressed in the Business Plan, is to:

- drive scientific and technological breakthroughs in the area of Molecular Medicine;
- seize potentially valuable economic opportunities in the healthcare (technology) sector by attracting investments, enabling (Dutch-based) corporation, SMEs and start-ups;
- deliver health care cost savings of at least EUR 1 billion annually in the Dutch health care system, reduce the overall mortality with 7000 deaths per year and increase the patients' quality of life, at the time the resulting innovations have been absorbed in clinical practice, all fully materializing between 6 to 10 years after the start of the projects.

Since the CTMM addresses pre-competitive research in the healthcare area, it will typically take 5 years after completion of the research project until new technologies and applications make their entrance into clinical practice. Applicants are expected to make quantitative projections on the expected clinical and economic impact of the proposed project in a Dutch context. More information about the objectives of CTMM, and the way in which the match of the project proposals is used in the evaluation procedure, can be found on the CTMM website (www.ctmm.nl), and in section “Selection procedure”, under the headings “Evaluation criteria” and “ISAC assessment”, of this announcement. On the website you will also find electronic versions of the business plan, the application form and a financial form for proposals. Applicants are advised to familiarize themselves with the CTMM objectives and the business plan.
Two types of projects are anticipated: a more clinically focused project predominantly addressing a particular disease, leveraging on one or more relevant technology platforms, or a project driven by a technological breakthrough that enables a novel approach in healthcare and is demonstrated in a translational clinical setting. The selected Disease Areas and Technologies are described below.

The Research Program:



Preferred project: combination of technological breakthroughs **and** translation into the clinic!

The scope of a CTMM proposal should fit into either one of the following alternatives.

I. Disease areas

The first alternative a CTMM proposal could fit into is to focus on one of the four following disease areas, in a translational setting.

1. Cancer

Within the translational oncology program, five themes will be addressed. The oncological disease types to be addressed are:

a. Breast cancer
b. Colorectal cancer
c. Lung cancer
d. Prostate cancer
e. Hematological malignancies

2. Cardiovascular diseases

The major cardiovascular disease types to be addressed in the Second Call are:

a. Vulnerable patient/instability of the atherosclerotic plaque
b. Cardiac failure
c. Sudden death
d. Diabetes mellitus
e. Stroke

3. Neurodegenerative diseases

The major neurodegenerative disease types to be addressed in the Second Call are:

a. Vascular dementia
b. Schizophrenia
c. Depression
d. Multiple Sclerosis

4. Infectious and autoimmune diseases

Priority will be given to those infectious diseases which:

a. have significant impact on morbidity and mortality
b. cause yearly local and/or international epidemics
c. have a high frequency of occurrence

Autoimmune diseases are a new disease area that was not mentioned in the first call for proposals. On the advice of the International Scientific Advisory Committee priority will be given to rheumatoid arthritis.

All disease focused proposals should also be based on and drive breakthroughs in one or more of the technology platforms described below. Integration of activities (e.g. stratification of patients through diagnostics, followed by localization through imaging, and following the result of therapy by quantitative imaging or with the help of biosensors) is recommended. For background information, please consult the business plan of CTMM on the website.

Please note that in the first call nine projects are funded in the areas of cancer, cardiovascular diseases and neurology. The project applications in the second call are not allowed to overlap with the content of the funded projects. For further details on these projects see our website www.ctmm.nl.

II. Technology platforms

The second alternative where a CTMM proposal could fit into is to focus on one or more of the following technology platforms. Also, these proposals have to be translational in character with impact on one or more of the four disease areas, and more than one disease type, mentioned above.

1.Molecular Diagnostics

Molecular biology and medical sciences are advancing to a point that human health and disease can be distinguished or traced to the molecular level. The objectives in this Technology Platform are:

1. Development of new bio-detection technologies for distinguishing molecular markers indicative of disease heterogeneity for specific diagnostics, prognostics and treatment follow-up;
2. Development of technologies for sensitive and rapid detection of disease-related molecular traces in (minute amounts of) body fluids or body tissue.

2.Molecular imaging

The objective in this Technology Platform is to advance molecular imaging from research to clinical application, particularly through:

1. Development of new types of agents (detection and therapy);
2. Optimization of imaging systems, scanning protocols and data processing tools with respect to (the use of) these agents in relation to detection and therapy.

3.Stratification of patients for evidence-based therapy

This Technology Platform will focus on what is needed for the identification of validated biomarkers for stratification of patients for individualized treatment. Requirements include determination of genomic or

proteomic profiles in relation to the selection of the most optimal therapy, the availability of technologies to measure the identified biomarkers, and the provision of an effective interface to the physician.

4.Imaging-guided and activated therapeutics

The objective in this Technology Platform is to develop and implement in the clinic improved approaches to drug delivery by applying advanced imaging and local activation technologies. In particular, the objectives are:

1. Improve stability of drug delivery systems in a biological environment;
2. Mediate the bio-distribution of active compounds;
3. Improve drug loading, targeting, transport, release and interaction with biological barriers;
4. Combine Molecular Imaging and drug delivery with Imaging-guided therapeutics.

Enabling technologies

Integration of “Enabling Technologies” and in particular of IT-infrastructure, within project proposals is important for CTMM. Despite the fact that ICT is not a prime goal of CTMM projects it is important to realize that the projects need adequate tools to perform their work and to minimize the operational burden for the projects. In the long run the objective of CTMM is to develop and implement a standardized and harmonized IT infrastructure as integral part of the research projects, if possible and if relevant. A pragmatic approach however should be used in the short term. To be able to assess the possibility and feasibility of a coordinated IT approach per project, proposals should describe the demand for IT infrastructure in terms of the anticipated benefits and costs. Areas to be covered in this description are:

- The requirements for the generic IT Infrastructure; the needs for data sharing between the partners in the project, interoperability of data management systems, type of data, data formats and ontology’s to be supported, computing capacity needed, communication infrastructure needs, security;
- The bioinformatics requirements for data mining and knowledge integration;
- Requirements for access to (licensed) content knowledge databases and reference data;
- Requirements for access to medical data in hospital information systems;
- A description of genomic and (medical) imaging data volumes;
- Specific software tools and support requirements.

Every applicant is asked to provide a contact person responsible for ICT issues. Projects that have already solutions in place or plan to implement specific solutions are invited to describe these explicitly.

Who can apply?

A proposal has to be submitted by a consortium of companies (at least one), academia and research institutes represented by a principal investigator (PI).

Participation of "non-Dutch" companies in the consortium is appreciated. The involved company/companies should carry out R&D activities in the Netherlands and have a Dutch office. A contribution to the project by a company not based in the Netherlands (maximum contribution 20% of the total industrial contribution) is permitted, provided that its contribution is key to the project and its expertise cannot be found nationally. Projects comprising "non-Dutch" companies should detail the contribution of these companies to the project and how their participation contributes to achieving the ambitions of CTMM.

The PI has a mandate from his/her partners to submit the proposal to CTMM. It is recommended that a PI with a strong track record in research as well as the capability to manage large consortia is appointed. A PI can manage only one CTMM project. All communications will go through the PI.

What can be applied for?

Proposals should specify how the proposed research fits within the priorities of the CTMM program. In the CTMM projects, industrial research (following the EU definition)[1] will be funded according to the Financial Guidelines CTMM agreed with the Minister of Economic Affairs, which is published on the CTMM website.

If a subsidy has been or will be granted by NWO or by the Commission of the European Union for the same project, the maximum amount of the total contribution of CTMM combined with that from NWO or EU may be no more than 60% of the total project costs. The PI is responsible to check on grants which are related to the CTMM proposal.
Note that CTMM IP rules overrule IP terms from all other project agreements. The IP rules are part of the Model Project Agreement, which is published on the CTMM website.
A research proposal should consist of a coherent project plan composed of several partners from academia and industry. The application form for proposals can be found on the CTMM website.
The proposal should have a minimum total budget (i.e. the total contributions from all partners and CTMM) of EUR 5 million and a maximum budget of EUR 15 million for a maximum period of 5 years.

Selection procedure

The Executive Board of CTMM will only accept a project for review if the proposal meets the eligibility criteria as stated below.
Eligible proposals will be reviewed and scored by (at least three) international experts. Applicants have an opportunity to propose possible reviewers on the application form. The reviews of the proposals by the peers will be sent (anonymously) to the applicants. The applicants are invited to respond to the comments made in the peer reviews. The project proposals, peer reviews and scores as well as the responses of applicants with respect to their peer reviews will be sent to the International Scientific Advisory Committee. Based on this information all projects will be ranked by the ISAC. The ISAC consists of experts with scientific and business backgrounds (Chair: Prof. Robert Reneman). ISAC members and peer reviewers will be instructed to review the proposals and advise the Executive Board in accordance with the objectives and criteria set for CTMM.

The Executive Board will consider the ranking advice of the ISAC in its final decision and propose a portfolio of projects to the Supervisory Board for final approval. The Executive Board will inform the PIs of the granted proposals, and negotiations will begin to conclude project and partner agreements.

Forms

The application form and the standard project budget form for proposals are available on the website of CTMM.

Eligibility criteria

The proposals should meet the formal criteria:

[1] Industrial research means that the planned research or critical investigation is aimed at the acquisition of new knowledge and skills for developing new products, processes or services or for bringing about a significant improvement in existing products, processes or services. It comprises the creation of components of complex systems, which is necessary for the industrial research, notably for generic technology validation, up to and including clinical phase IIA (proof-of-concept) but excluding prototypes.

1a. the proposal should *address one of the four diseases areas* and should be based on and drive breakthroughs in one or more technology platforms. Or
1b. the proposal should address *one or more of the technology platforms* and apply to one or more of the disease areas and more than one disease type;
2. The proposal should be *translational in character* (from bench to bedside);
3. The *funding by industry and by academia is quid pro quo*[2]. Also, the project is jointly executed by public and private partners.

Compliance with the formal criteria will be assessed at the CTMM program office.

Evaluation criteria

For the evaluation and selection of eligible proposals, the following criteria will be applied:

Top quality research (weight: 50%)

- Scientific excellence of medical, clinical and technological research
- Innovative character of the project
- Breakthrough clinical and technological potential of the project
- Effectiveness of the research design and methodology
- Coherence of program and justification of the role of the participating partners
- Track record and international standing of key partners in the relevant areas (clinical and technological)
- Feasibility of the project goals within the timeframe and budget

The total weight of the following economic and clinical potential criteria will be 50%.

Economic value creating potential

- The economic benefit for Dutch industry (description of the economic value of the expected research results for (future) involved industry)
- Generating foreground IP with commercial valorization potential
- Generating products with commercial value
- Stimulating new entrepreneurial activity
- Knowledge dissemination

Clinical value creating potential (including Medical Technology Assessment (MTA))

- The clinical benefit for the healthcare system including the net financial value for the Dutch healthcare system (description of the clinical value of the expected output of the project in qualitative and quantitative terms based on an MTA assessing the integral impact of the project).
- Leading to improvement of (early) diagnosis and/or treatment of the patient
- Knowledge transfer to the healthcare system
- Method of monitoring the progress in terms of goals and milestones, related to the envisioned cost/benefit as described in the MTA.

[2] Contribution of the partners can be in kind or in cash, where funding by industrial partners has to consist of at least 50% in cash. An exception is made for small companies (< 20 FTE); they are allowed to contribute 100% in kind. However, the total cash contribution of all industrial partners has to meet the 50% criterion for the project as a whole.

The peer reviewers are asked to provide their opinion, comments and motivation on all three criteria. Additionally, they are asked to mark the proposal on all three criteria and an overall evaluation with a "outstanding", "very good", "good", "mediocre" and "poor". (Score 5 – 1)

For approval, projects will have to score positive for each of the three sets of criteria listed (positive score: average score of 3 (out of 5) or higher; when a project proposal scores lower than 3 at one or more of the criteria, it will be excluded from the ranking procedure).

ISAC assessment

This paragraph describes the assessments of research projects in the second call for proposals of the Center for Translational Molecular Medicine (CTMM). The International Scientific Advisory Committee (ISAC) of CTMM has a crucial role in selecting the proposals that will be supported within the CTMM program.

The ISAC will rank the project proposals and provide a written opinion on each of the evaluation criteria (and – if applicable – on overlap with approved proposals from the first call). The proposals will be ranked in five categories (4 disease areas and technology), such that the CTMM executive board can select the best proposals per area. The disease areas are cancer (20 - 30 % of the budget), cardiovascular diseases (20 - 30% of the budget), neurodegenerative diseases (10 - 25% of the budget) and infectious and autoimmune diseases (10 - 25% of the budget).Technology platforms will be allocated 20 – 30% of the budget.

Not only is the ISAC asked to rank the proposals, but also to give an indication about the quality of the proposals, per evaluation criteria and overall by marking them with "outstanding", "very good", "good", "mediocre" or "poor". The executive board will use these qualification marks in order to decide if the whole budget will be granted. None of the projects marked with a qualification less than good will be granted budget.

The ISAC is requested to prepare a summary report containing

- The anticipated impact of the by the ISAC proposed portfolio in the light of each of the overall ambitions of CTMM which are listed above;
- A clear answer to the question whether or not the proposed portfolio will lead to the realization of all overall ambitions of CTMM, taking into account the availability of only part of the requested budget;
- Recommendation on which steps are necessary to ensure the realization of the over-all ambitions of CTMM, on top of the portfolio proposed following the First and Second Call.

The CTMM office will support the ISAC and the evaluation process. The CTMM office will provide the ISAC with (digital) copies of all research proposals, the peer reviews and a summary of both. The CTMM will collect and document the assessments provided during the ISAC meeting.

Before the meeting the members of the ISAC will be asked to formulate their preliminary opinion on the proposals by giving grades from 1-5 (preferably with comments) on each criterion for each proposal. The CTMM office plans to receive this information at least 5 days before the ISAC meeting.

During the ISAC meeting the final rankings will be generated. This will be discussed in a plenary session. The secretariat provides the ISAC with an overview of the collected opinions of the individual members and a provisional ranking.

All research proposals will be discussed, In case of crucial questions arising during this discussion the principal investigator of a project will be contacted by the ISAC, and all members of the ISAC are given the opportunity to adjust the ratings according to the information provided during the discussion. The final ranking(s) has to be agreed upon by a majority of the members.

The CTMM office will collect the final comments. All members have to agree on the comments and the ranking and the chair will sign the overall comments and the ranking of the project proposals.

Intellectual Property (IP) and Partner & Project Agreement

CTMM has developed a Model Project Agreement which is non-negotiable and has to be used for all CTMM projects. Part of the Project Agreement is dedicated to the CTMM IP rules governing ownership, protection, commercial - and research use, and dissemination of IP. The IP rules were prepared by CTMM following thorough consultation with industry, knowledge institutes and primary stakeholders – such as VSNU and NFU which play a major role in the creation and management of IP.

The Model Project Agreement will contribute to streamlining much of the legal process and speed up negotiations, thus minimizing costs incurred by partners.

CTMM requires all participants in CTMM projects to sign a Partner Agreement. The Partner Agreement deals with general issues (terms and conditions) of the CTMM research program which are non-negotiable as well. A Model Project Agreement forms part (annex) of the Partner Agreement.

The Model Partner- and Project Agreements are published on the CTMM website.

Practical information

The deadline for submitting proposals for CTMM 2008 is November 30, 2008. All proposal forms are to be completed and sent to CTMM according to the following procedure:

- Submit all information via email to secondcall@ctmm.nl (stating your proposal's title and acronym as subject)
- An application has to comprise of (at least) the following information to be complete:
    - Application form (Word format)
    - LOI's of each project partner (pdf format)
    - Appendices B/C/D/E of the application form (pdf format)
    - Budget form (completed tabs of Excel sheet)

  The application- and budget forms have to be submitted in the original formats (Word/Excel) since they will be processed further by CTMM.
- CTMM will send an email reply to confirm receipt of your application. A paper-copy of this statement, signed by the PI, has to be returned to CTMM.
- For questions regarding your application, please also use secondcall@ctmm.nl

The overall budget of the Second Call is EUR 150 m, with a CTMM-contribution of EUR 75 m (i.e. 50% of the total project costs). This budget is distributed over 5 research categories (see section 'ISAC assessment'). From the research budgets, 5% of the total project costs will be reserved to cover cost of knowledge dissemination, program management and support by the CTMM office.
The CTMM office intends to inform all applicants about rejection or approval of their proposals before April 1, 2009.

Budget information

The IOP-TTI subsidy rules differ from other subsidy programs. The Government pays its subsidy to the CTMM Foundation, and not to the individual partners or PIs. The (industrial) partners in the projects have to pay their contributions to CTMM as well, and not to the consortium. CTMM uses its funding (subsidy plus partner contributions) to compensate the individual partners for their respective project costs. For more information on the CTMM financial model, please refer to the document "CTMM Financial Guidelines".

In practice, this means that the partners in a project invoice CTMM for their part in the total project cost, and CTMM pays the invoice to the partner with its funding. On the other hand, CTMM invoices each partner for its cash/in kind contribution. Cash contributions (industry) will be paid to CTMM. In kind contributions will be set off against the initial invoices sent to CTMM by the partners.

For the call, a standard financial form has been developed to calculate the project budget and the project funding. The form is divided into two parts. The first part of the sheet calculates in several separate tabs the "project cost specified per work package. As mentioned above, 5% of the total project cost is added to cover the cost of knowledge dissemination, management and support by the CTMM office. CTMM contributes 50% of the sum of the total project cost and the 5,3% markup[3].
The remainder of the total cost has to be covered by cash and in kind contributions of the partners in the project.

Eligible costs

The IOP-TTI subsidy rules specify the following research costs that are eligible for subsidy:

A. *Cost of personnel, as far as these are directly necessary for the research to be performed*

Man hours should be calculated using the uniform calculation method for hourly tariffs. These tariffs are calculated in the project budget form, and comprise:

- Actual cost of wages (including social security and cost of pension plans);
- A markup of 50% of the actual cost of wages to cover indirect costs;
- A fixed fee of EUR 15,000 to cover direct cost of (technical) support and supervision (i.e. a fixed amount of EUR 10,000 direct wage increased by a 50% markup to cover indirect costs);
- A bench fee of EUR 15,000 to cover all consumables, travel, and other out-of-pocket costs.

B. *Cost of materials and services*

- Cost of consumables, based on actual purchase price. Cost of consumables can only be accounted for so far as they exceed the bench fee of EUR 15,000.
- Cost of involvement of third parties.

C. *Cost of usage of existing equipment and infrastructure of the partners*

Tariffs on equipment or infrastructure should be calculated using the partner's internal cost price method (excluding gross margin).

D. *Cost of new equipment to be purchased (investments)*

For more details on eligible investment costs, please refer to the project budget form.

Follow-up of the projects

For the proposals that are selected, the Partner Agreements and Project Agreements have to be signed by all project partners, and the budget will be specified by the CTMM office. This process must be completed before the projects can start.

[3] 5% of the **total** project costs corresponds to 5,3% (5/95) of the project costs of the partners, so the markup is 5,3%

Each consortium will provide at least one progress report a year to CTMM. Each year, a financial and project overview must also be submitted for review. There will be a midterm review, at which point a go/no go decision is made for the second part of the project. External reviewers will be involved in the midterm review.

CTMM will provide 50% of the yearly project expenses every year to each of the project partners up to 80% of the total project costs. When the project is finished, the total expenses have to be assessed by an accountant and the final 20% can be calculated. CTMM will provide an easy to use Internet-based application for time registration that has to be used by all researchers who perform research for CTMM projects.

Confidentiality

CTMM ensures that only the members of the International Scientific Advisory Committee, peer reviewers, the CTMM Executive Board, the CTMM Supervisory Board and employees at the CTMM office will have access to the proposals. CTMM employees and the CTMM boards have all signed a non-disclosure agreement. Peer reviewers will also be asked to sign such an agreement.

Planning

November, 30 2008	- Closing of the call
December, 1-5 2008	- Check formal criteria and completeness of the proposals by CTMM office
December, 5-19 2008	- Proposals will be sent to peers reviewers. - Peer review
December, 22 2008 - January 9 2009	- Comments from applicants
January 09- 15 2009	- Preparation of data pack for the ISAC members
January, 16 2009	- ISAC is provided with all data: applications, peer reviews & comments from the applicants on reviews
February, 13-16 2009	- ISAC review
March 1-31	- CTMM office finalizes the advices per proposal. CTMM Supervisory Board reaches agreement on the project portfolio

Contact

For further information, please contact:
Center for Translational Molecular Medicine
High Tech Campus 12a
NL-5656 AE Eindhoven
the Netherlands
T. +31(0)40 27 74 110
E-mail: secondcall@ctmm.nl
www.ctmm.nl