Publications of the Academy of Finland 1/07

Microbes and Man Research Programme 2003–2005 (MICMAN)

Evaluation Report

Academy of Finland
Research funding and expertise

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Evaluation Report

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Contents

Kuvailulehti

Julkaisija	Suomen Akatemia	Päivämäärä 14.11.2006
Tekijä(t)	Mikrobit ja Ihminen tutkimusohjelman arviointipaneeli: Guy R. Cornelis (puheenjohtaja), Ann-Mari Svennerholm, Robert B. Sim, Gunna Christiansen	
Julkaisun nimi	Microbes and Man Research Programme 2003-2005 (MICMAN). Evaluation Report	
Tiivistelmä	Suomen Akatemia ja Ruotsin Strateginen Rahasto käynnistivät yhdessä vuonna 2002 Mikrobit ja Ihminen -tutkimusohjelman, joka toteutettiin vuosina 2003-2005. Ohjelman tavoitteena oli tuottaa tietoa mikrobin ja isännän vuorovaikutuksesta ja hyödyntää tätä tietoa ihmisen terveyden ylläpidossa ja sairauksien ehkäisyssä ja hoidossa. Vuonna 2005 Suomen Akatemia nimitti kansainvälisen asiantuntijapaneelin arvioimaan ohjelmaa. Arvioinnin tavoitteena oli tarkastella erityisesti ohjelmakokonaisuuden toteutumista, kansallista ja kansainvälistä (erityisesti suomalais-ruotsalaista) yhteistyötä ja verkostoitumista, tutkimuksen tieteellistä tasoa, tutkijankoulutusta ja -vaihtoa, ohjelman lisäarvoa, tulosten sovellettavuutta sekä antaa suosituksia tulevaa toimintaa varten. Paneeli arvioi tutkimusohjelman olleen tieteellisesti menestyksellinen, sillä se tuotti runsaasti uutta tietoa. Tiedon suoraa käytännön soveltamista ei odotettu, koska ohjelma oli suhteellisen lyhytkestoinen. Tutkimusohjelma oli hyvin suunniteltu ja se tuotti useita hedelmällisiä yhteistyösuhteita. Erääät suomalais-ruotsalaiset konsortiot olivat erittäin menestyksellisiä. Tutkijankoulutukseen ja -vaihtoon panostettiin merkittävästi. Monitieteisyyden taso vaihteli eri projektien välillä. Kaiken kaikkiaan tutkimusohjelman taso arvioitiin erittäin hyväksi. Paneelin keskeisiä suosituksia ovat mm: ohjelmakauden pidentäminen 3+2(3) vuoteen väliarvioinnilla; väitöskirjantekijöiden rahoituksen turvaaminen neljäksi vuodeksi; kansainvälisen yhteistyön vahvistaminen; nuorten tutkijoiden liikkuvuuden edistäminen; tutkijakoulujen luominen tutkimusohjelmien ympärille; uuden tutkimusohjelman avaaminen liittyen luonnolliseen immuniteettiin, tulehdukseen, kroonisiin infektioihin ja infektioiden systeemibiologiaan.	
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Description

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Author(s)	Evaluation Panel of the Microbes and Man Research Programme: Guy R. Cornelis (chair), Ann-Mari Svennerholm, Robert B. Sim, Gunna Christiansen	
Title	Microbes and Man Research Programme 2003-2005 (MICMAN). Evaluation Report.	

Abstract	The Microbes and Man research programme (MICMAN) was launched by the Academy of Finland and the Swedish Foundation for Strategic Research in 2002 and implemented during 2003-2005. The specific objective of the MICMAN programme was to increase our understanding and knowledge of the interaction between host and microbes, and to apply this knowledge to the maintenance of health and to prevention and treatment of diseases. In 2005, the Academy of Finland appointed an international expert panel to evaluate the programme. The panel was asked to assess the programme as a whole and reflect especially the following issues: Implementation of the programme, collaboration and networking on national and international levels (especially the Finnish-Swedish collaboration), scientific quality and innovativeness of the research, contribution to researcher training and exchange, added value, applicability of research results as well as recommendations for the future. The panel found that scientifically the programme was a success, since substantial new knowledge was acquired. A direct application of this knowledge was not to be expected from relatively short-term programme. The programme was well planned and it created several fruitful collaborations. Some of the Finnish-Swedish consortia were very successful. A significant effort was made towards training and exchange of researchers. The level of multidisciplinarity varied between the projects. The overall quality of the programme was considered very good. The key recommendations of the panel are the following: to extend the programme period to 3+2(3) years with a mid-term evaluation, secure funding for PhD students for 4 years, stronger promotion of international collaborations, an increase in mobility of young researchers, building of graduate schools around national programmes, and new research programme(s) related to innate immunity, inflammation, chronic infections, and system biology of infection

Key words	Research programme, evaluation, research funding, microbes, microbial, host, interactions, health, disease	
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Preface

In 2002, the Academy of Finland together with the Swedish Foundation for Strategic Research (SSF) established the Microbes and Man Research Programme (MICMAN) to support high quality research related to interaction between host and microbes in the fields of health research, biosciences and environmental sciences.

The main objectives were to increase our understanding and knowledge of the interaction between host and microbes, and to apply this knowledge to the maintenance of health and to prevention and treatment of diseases.

MICMAN was conducted over a period of three years (2003-2005). It consisted of 15 research projects and consortia that covered a wide range of topics and disciplines. The total funding of the programme amounted to 5.4 million euros.

In October 2006, Academy of Finland and the Swedish Foundation for Strategic Research convened an international evaluation panel to review the programme. The members of the panel were:

- Professor Guy R. Cornelis, Infection Biology, Biozentrum, University of Basel, Swizerland (chair),
- Professor Ann-Mari Svennerholm, Institute for Medical Microbiology/Immunology, University of Gothenburg, Sweden,
- Professor Robert B. Sim, MRC Immunochemistry Unit, Department of Biochemistry, Oxford, United Kingdom and
- Professor Gunna Christiansen, Department of Medical Microbiology and Immunology, Aarhus University, Denmark.

The evaluation panel had a two-day meeting in Helsinki. During the meeting the panel had the opportunity to interview some of the project leaders, doctoral students and the programme manager. The evaluation report is based on the written material produced for the evaluation and the interviews.

November 2006,
Guy R. Cornelis
Professor, Chair of the Evaluation Panel

1 The MICMAN research programme

1.1 Background

The initiative to establish the Microbes and Man Research Programme, MICMAN, had come from researchers working in the fields of medicine, nutrition research and environmental research in Finland. In response to this initiative, the Academy of Finland hosted an exploratory workshop on the subject of *Microbes and Man: Health, Nutrition and Environment* in August 2001. During the workshop several relevant research needs were identified, and this information was used as a basis for the preparation of the programme.

The first negotiations between the Academy of Finland and the Swedish Foundation for Strategic Research (SSF) were held in autumn 2001. As a result of the positive discussions, joint planning of the content of the programme began in a meeting of the representatives of the funding organisations in February 2002. The main themes were defined and a draft of the Programme Memorandum prepared. The Memorandum (including the call text) was finalized in March 2002, and published on the homepages of both organisations on April 1, 2002. The establishment of this funding collaboration was confirmed by an official agreement between the Academy of Finland and the SSF signed in November 2002.

1.2 Objectives

The main objective of the MICMAN was to increase our understanding and knowledge of the interaction between host and microbes, and to apply this knowledge to the maintenance of health and prevention and treatment of diseases. According to the definition of the Programme Memorandum the programme aimed to increase understanding of

- the development, composition and health effects of the resident microflora under the influence of both host and environmental factors, including nutrition of the host and effects of individual food components,
- the host-microbe interactions in the development and course of diseases and their sequelae and
- the ways in which microbes and/or their metabolites in the environment influence human health.

The research supported by the programme was expected to take advantage of the technological and knowledge bases of the postgenomic era. The programme was seeking to generate multidisciplinary networks of microbiological research and to promote researcher training and exchange. International contacts were an integral part of both the research programme and the research teams involved.

The enhanced activity in basic research was expected to underpin the advancement of applied research. A further objective of the programme was to strengthen cooperation between universities and research institutes, and to facilitate the practical application of research findings.

The aim of the Finnish-Swedish collaboration was to promote networking and training of researchers as well as to increase scientific quality of research.

1.3 Basic information on the programme

Organisation

The Board of the Academy of Finland appointed a Steering Programme Committee for the years of 2002-2003 (see Appendix 2) to plan the research programme, and a subcommittee to make the funding decisions of the Academy of Finland. All decisions of the Swedish Foundation for Strategic Research were made by the Foundation's board. The Steering Committee, composed of members representing the funding organisations and an additional expert, was most active at the onset of the research programme.

The programme had a joint coordination. After a tender, the coordination of the programme was contracted to the National Public Health Institute. Dr Soile Juuti was appointed as a full-time programme manager. The aim of the coordination was to support and advance the objectives of the programme, and to implement the scientific and administrative coordination of the programme. The programme manager was supposed to promote interaction between the projects, plan doctoral level education and internationalisation, advance collaboration with the other national and international research programmes, and communicate on the programme and its results in the domestic front and abroad. In addition, the programme manager participated in the planning and application procedures of the programme and prepared the material for the programme's final evaluation.

The Academy of Finland and the Swedish Foundation for Strategic Research participated in the ERA-NET PathoGenoMics (2004-2009) project funded by the EU 6th FP (*www. pathogenomics-era.net*). The working time of the programme manager of the MICMAN was shared between the ERA-NET project and the MICMAN programme.

Programme funding

The total funding of the programme amounted to 5.4 million euros. The share of the Academy of Finland was 4.1 million euros, and that of the Swedish Foundation for Strategic Research 1.3 million euros. This was the first time that these two funding agencies collaborated in a joint research programme.

Application process

In all 96 plans of intent were submitted to the call. The Steering Programme Committee evaluated them and selected those that were invited to the second application round. These 28 full applications were evaluated by a panel of international experts:

- Prof. Ingolf F. Nes, Agricultural University of Norway, Norway,
- Prof. Jörg Hacker, Institut für Molekulare Infektionsbiologie, Universität Würzburg, Germany,
- Prof. Robert B. Sim, MRC Immunochemistry Unit, Department of Biochemistry, Oxford, UK,
- Prof. Daniel Lew, Chief Infectious Diseases Division, Geneva University Hospital, Swizerland,
- Prof. George T. Macfarlane, University of Dundee, MRC Microbiology and Gut Biology, UK.

The evaluation statements prepared by the expert panel were sent to the Programme Committee, which suggested the applications to be funded. The funding decisions were made by the subcommittee of the Academy of Finland and the board of the SSF. 15 research projects or consortia gained funding; five of them were Finnish-Swedish consortia, two were Finnish consortia and eight were individual Finnish projects. Altogether 21 Finnish and 7 Swedish research groups were funded. They represented 11 universities or research institutes. A list of projects and information on their funding are given in Appendix 1.

2 Evaluation procedure

The aim of the evaluation was to estimate to what degree the MICMAN research programme has succeeded in fulfilling the objectives originally set for it. Evaluation also aims to provide feedback on the success of the programme and its coordination as well as other information that is useful for purposes of science policy planning and decision-making.

Of specific interest in the evaluation were the programmatic approach, added value, internationality, multidisciplinarity, training, networking, and applicability of the results. The panel was expected to assess the programme as a whole and reflect especially the success/failure concerning the following issues:

1. Implementation of the programme.
– Preparation and planning the programme
– Funding decisions of the research projects in creating the necessary preconditions for the programme
– General functioning of the programme
– How the programme objectives were met
– Enhancement of multidisciplinarity in research
– Scientific and administrative coordination

2. Collaboration and networking on national and international levels, especially the Finnish-Swedish collaboration of the programme.

3. Scientific quality and innovativeness of the research

4. Contribution to researcher training and exchange

5. Added value of the programme

6. Applicability of research results

7. Recommendations for the future (including justification for the recommendations)

The researchers who took part in the programme assessed the programme's general success as well as their own contribution with self-evaluations (Appendix 3).

In addition, the researchers submitted final reports including a short abstract. The deadline for all report material was March 31, 2006.

The steering programme committee was responsible for the general planning of the evaluation. The programme manager organized the programme's self-evaluation, compiled and prepared the material, and was responsible for the practical implementation of the evaluation.

The evaluation panel had access to the documentation produced on the MICMAN programme and the final reports of each MICMAN funded project (see Appendix 4). The material for the evaluation was sent to the panel members in August 2006, which gave them two months to get familiar with it. The panel had a joint meeting at the Academy of Finland in October 2006 (Appendix 5). For this meeting, two evaluators prepared draft evaluations of each project and the panel used these as a basis in discussions and interviews. Interviews, with altogether seven project leaders and four PhD students, gave further general insight to the programme.

3 Evaluation results of the programme

3.1 Implementation of the programme

Preparation and planning the programme
The panel of reviewers considered that the programme was very well prepared and planned.

Funding decisions of the research projects in creating the necessary preconditions for the programme.
The funding decisions were considered to be good. However, it appeared that some fields of infection-biology were under-represented in the final MICMAN programme. This may have different causes which could become apparent from analysis of the early applications and the first round of selection. Such analysis by the panel would be facilitated if the first rounds of selection were more transparent. Although this would obviously have been an additional constraint, the panel thinks that every decision of rejection made during the pre-selection procedure should ideally have been accompanied by a short motivation. This document could have been added to the documents provided for the final evaluation. It might have allowed the panel to understand why some fields are under-represented in MICMAN.

The under-represented fields were virology and parasitology. Although the new discipline of "cellular microbiology" is presently blooming worldwide, it was not very much represented in MICMAN. The panel also noted that none of the most deadly infectious diseases worldwide (acute respiratory infections, AIDS, diarrhoea, tuberculosis, malaria) was specifically studied. Thus, although many important aspects of the man-microbe interaction were studied, the balance between the different aspects was not fully representative of the field.

General functioning of the programme
The researchers were unanimously very positive about the management by Dr Soile Juuti. According to several researchers, Dr Juuti was instrumental in implementing fruitful collaborations.

Realisation of the programme objectives
As far as basic knowledge is concerned, the programme was a success. Substantial new knowledge relative to the interaction between host and microbes was acquired.

Some projects, though not many, took great advantage of genomic data. One multidisciplinary project involved a strong bioinformatics analysis of the human genome. In contrast, there was little implementation of the new proteomics approaches.

The level of multidisciplinarity varied between the different projects but several projects combined complementary expertises in a remarkable way and gained success. The panel considers that these three years of contact were very favourable to the generation of multidisciplinary collaborations for many of the projects and that new collaborations are expected to emerge from MICMAN in the near future.

Scientific and administrative coordination
This part was considered outstanding. The programme manager Dr Soile Juuti created the conditions for optimal collaboration within the consortia and within the programme. This kind of coordination could be taken as an example for other networks.

3.2 Networking on national and international levels

Finland contributed almost 80 % of the financial resources of MICMAN and so more Finnish researchers were included than Swedish. Unfortunately, several of the Swedish leading groups in the field were not part of MICMAN. Nevertheless, Swedish participants expressed their enthusiasm about this joint programme. Some of the bi-national consortia were very successful, meaning that the idea of bi-national programmes is to be encouraged. However, the distortion between the weights of the two partners within MICMAN weakened the initiative. The panel regrets this distortion and considers that to achieve a fully collaborative programme, the financing should be at a more comparable level, on both sides.

Besides the Finnish-Swedish contacts, there were additional international contacts of the projects but these could have been more extensive and numerous.

MICMAN clearly strengthened the cooperation between universities and research institutes within Finland. These collaborations are very likely to last beyond the MICMAN funding period.

3.3 Scientific quality and innovativeness

The funding was allocated to projects with different levels of ambitions. In some cases, the funding was used to set the bases to address ambitious questions requiring long term-investment. For example, this is the case of the project on group A *Streptococci*, which will only pay off in a year or two but is extremely interesting. In other cases, the goals were not so ambitious but in these cases, the final results turned

out to be closer to applicability. Project evaluations in detail are presented in paragraph 4.

Overall, the quality of the programme is considered very good. Some projects were truly innovative and multidisciplinary.

3.4 Contribution to researcher training and exchange

A significant effort was made towards training and exchange of researchers. The annual MICMAN meetings were very much appreciated and they were instrumental in promoting contacts and exposing young researchers to multidisciplinarity. Workshops were organized within the different consortia and they turned out to be very fruitful for the exchange of results and the generation of new ideas. The organization of the annual "Microbial pathogenesis day" was an excellent initiative, fully appreciated by the PhD students. The panel recommends this excellent initiative be pursued. Some PhD students visited another laboratory participating in the programme but the panel's opinion is that these exchanges could have been more extensive and numerous. Many PhD students were offered the opportunity to attend international conferences. One student financed by the programme participated in the EMBO international summer course on Molecular and Cellular Biology.

The panel considers that the PhD students clearly benefited from MICMAN. However, the panel thinks that even more could be done for their education, in the broader sense (see recommendations, paragraph 5).

3.5 Added value of the programme

Complementary expertises were combined in projects, resulting in several cases in excellent added value. A collaborative dynamic was initiated and it is expected to have long-term beneficial outcome. The coordination of the programme also added value in that the communication and annual symposia gave increased opportunities for dissemination of ideas and opportunities for media coverage, which would otherwise not have occurred. Meetings generated new ideas coming from multidisciplinary interactions and new projects are now being implemented.

The panel acknowledges that information to the public has been excellent and should be taken as a model for future programmes.

3.6 Applicability

A direct application of this knowledge to the maintenance of health and the prevention and treatment of diseases was not to be expected from such a short-term programme. There are good reasons to believe that some results will, however, be translated in the near future. Some projects came close to that. Among others, the panel would like to cite that novel diagnostic tools could be developed to diagnose *Borrelia* infections. Some putative protective antigens for inclusion in vaccines have been identified. The link between exposure to microbes during childhood and allergy was deepened, which opens a promising avenue for the development of probiotics aiming at the prevention of allergy. There are thus good examples where the research will be followed by applications. Despite these examples, it must however be mentioned that there were not many initiatives towards application of the research results.

4 Scientific evaluations of the research projects

The Evaluation Panel assessed all the 15 projects (Appendix 1) involved in the Research Programme on the basis of the extended abstracts and final reports of the projects. In addition, further general insight was obtained in discussions with project leaders (although not all project leaders were interviewed). Some groups had a long working history on the topic of their project, while others just started it in this programme. Many of the projects continued their work after completion of the MICMAN funding period and many key publications and doctoral dissertations were still in preparation. For these reasons the final impact and applicability of the results cannot be assessed as yet.

Project 1. BACTERIAL: EPITHELIAL CROSS-TALK AND ESTABLISHMENT OF THE MUCOSAL IMMUNE SYSTEM
William Agace, Associate Professor, University of Lund, Sweden.
Catarina Svanborg, Professor, University of Lund, Sweden,
Mary Jo Wick, Professor, Goteborg University, Sweden,
Sirpa Jalkanen, Academy Professor, University of Turku, Finland,
Mikael Skurnik, Professor, University of Helsinki, Finland

The project represents a strong consortium with five internationally very well recognized project leaders, two from Finland and three from Sweden, the coordinator being active at the University of Lund. An ambitious research project was the basis of the funding. The overall aim was to analyze the bacterial-epithelial cell interactions in the establishment and modulation of mucosal leukocyte populations of importance for mucosal immune defence.

The consortium has arranged annual meetings with all the participating research groups. In spite of the consortium receiving substantial funding for networking and including top-ranked scientists, joint project activities have been limited. On the other hand, most of the group members have appreciated the coordination meetings, chances for exchange of ideas etc. and there is optimism that the MICMAN programme may lead to increased interactions between the different groups in the future. Indeed promising collaborations have already been initiated between some of the project leaders during the MICMAN project period and there has been some transfer of technology between the different groups. Each individual group of the consortium has produced research of high scientific quality, and their work has resulted in several good publications in internationally well or very well recognized journals. The potential for commercializing findings derived from research within the consortium has not, with some exceptions, been highlighted.

Subproject Agace
In vivo models were used to study the response of mucosal cells to bacteria and to analyze the subsequent leukocyte subset recruitment to the mucosal surface. It was found that the gut dendritic cells were important for generation of gut tropic T cells in particular dendritic cells 103+. Imprinting of these T cells may be influenced by the bacterial flora.

The research is of a very high scientific quality. The results have also potential commercial value and contacts with industry have been made to further develop findings. The project coordinator has also been successful in attracting prestigious grants from other sources (e.g. an *Ingvar Carlsson grant* from SSF and support from the *Wellcome Trust*). The Agace group has been very productive with 12 publications, 4 of which result from the MICMAN funding. In addition 2 reviews (out of 6) resulted from the funding. Patenting of the results is possible in future. One PhD student and one postdoc have benefited from the support from MICMAN. The project leader is optimistic that the MICMAN project will lead to enhanced collaboration with other project groups within the consortium.

Subproject Svanborg

This group is studying bacterial:epithelial cross-talk using urinary tract infections as a model. The group has studied the pathogenesis of this disease for more than 25 years and has published numerous scientific papers. Professor Svanborg is an international leading authority in the field of bacterial epithelial cross-talk and the contributions from her group during the project period are impressive. However, the funding for her contribution from MICMAN has been very limited and has only allowed partial funding for a postdoc from Finland. During the project Svanborg et al. produced 11 publications on the subject focusing on the role of TLR4 in knock-out mice, and chemokine responses in humans with febrile urinary tract infections.

The main benefit for this group has been increased possibilities for networking with other parts of the consortium.

Subproject Wick

In this group the bacterial:epithelial cross-talk is studied using a *Salmonella*:gut model to study homing of *Salmonella*-recruited monocytes to gut-associated lymphoid tissue in antibody blocking studies. The project is performed in collaboration with the Jalkanen group, Turku, Finland. Unfortunately, this collaboration just started to be productive when the programme finished. The Wick group also collaborated with the Agace group to whom their Salmonella model has been transferred. The Agace LCM and RT-PCR methods have been transferred from Agace to the Wick laboratory.

The result of the MICMAN supported project is one submitted article and some book chapters, but no joint publications with other members of the consortium have been published yet. However, the group has published several papers in very good journals and has been acting in the training of several PhD students, one of whom has participated in the MICMAN programme. The project leader has greatly appreciated the networking meetings offered within the consortium, but she is critical of the short duration of the project that has not allowed completion of objectives.

Subproject Jalkanen

This group works with the vascular adhesion protein-1,VAP-1/AOC3, and its role in lymphocyte migration. They have created AOC3/VAP-1 KO mice and used these mice to analyze lymphocyte trafficking using intravital microscopy. They found that trafficking to Peyer's patches was reduced and that there was a slight reduction in lymphocyte homing to mesenteric lymph nodes and spleen. In collaboration with the

Skurnik group they have infected these KO mice and controls with *Yersinia*, but no additional infection was seen in the KO mice. Therefore, the group has been searching for compounds that may block enzymatic activity of VAP-1 and found that certain aminoglycoside antibiotics can do so.

One post doc from Jalkanen's group spent a year in the Svanborg laboratory and a Japanese scientist visited the Jalkanen group (MICMAN funded) and transferred the intravital microscopy technology. The MICMAN funded project has resulted in one publication with other members of the consortium and some manuscripts are in preparation. Two book chapters and two manuscripts dealing with inhibition of AOC3 have also been produced. Jalkanen's group has benefited from collaboration mainly through the joint meetings between the Finnish and Swedish groups and by the training of a postdoc from her group in a Swedish laboratory (Svanborg's).

Subproject Skurnik

This group is studying the interaction of *Yersinia enterocolitica* with the serum complement system. The serotype Ye O:3 resists the complement mediated bactericidal activity of human serum. To identify bacterial factors responsible for this effect they made 23 mutant strains of Ye O3 with combinations of deletions of the adhesin YadA, the invasion protein Ail and the O-ag and outer core. Yad was the most potent, O-antigen the least, in combination with any of the others. The regulatory factor H of the complement system was also studied and since factor H binds to to YadA 30 mutants of different parts of YadA were constructed for further analysis.

Skurnik's group has mainly collaborated with other Finnish groups and the Göteborg group (Mary Jo Wick). The project has resulted in one co-publication with the Jalkanen group. In addition Skurnik et al. have been very productive and published numerous studies, often in very good journals. Two publications, out of 17 since 2003, are directly related to MICMAN. There is no commercial exploitation or contact. MICMAN has provided funding and has allowed training of one PhD student; it has also supported much appreciated networking by arranging consortium meetings etc.

In conclusion this consortium successfully participated in the MICMAN programme but due to the short time frame the interactions were limited.

Project 2. REACTIVATION AND IMMUNE EVATION OF BORRELIA INFECTION

Sven Bergstrom, Professor, University of Umeå, Sweden.
Matti Viljanen, Professor, University of Turku, Finland.
The consortium had the additional participation of Professor **Seppo Meri**, Haartman Institute, University of Helsinki, Finland.

Subproject Bergstrom

Borrelia differs from other bacteria by being shaped as a spiral, having linear chromosomes and having two different hosts: the ticks with no adaptive immune system and humans with an adaptive immune system. The aim of this study was to gain insight into the virulence properties of *Borrelia*. They have determined the

integrin-binding protein P66 (Oms66) to be a channel-forming protein of the outer membrane and characterized its function. To study adhesion of *Borrelia* to human erythrocytes they used a rosette-forming strain of relapsing fever Borrelia species and identified a 27 kDa *Borrelia* protein that binds to human erythrocytes. They further studied the host proteases used by *Borrelia* to spread infection, and they used a murine model to study how *Borrelia duttonii* affects the outcome of pregnancy. This model was also used to study reactivation of infection. Their plans for projects to be performed in the future will depend on EU funding and will elaborate on serum sensitivity, include studies on whether a bird isolate of *B. garinii* can infect humans, genetic differences and gene transfer between the isolates. The group had excellent collaborative work with Seppo Meri's group on complement protein-*Borrelia* interaction.

Subproject Viljanen

This group has studied gene expression in dendritic cells DC upon infection with *B. burgdorferi* and compared the resulting microarray data to data of DC stimulation with LPS. Interestingly, it was found that *Borrelia* did not upregulate CD38 (a central player in chemotaxis of DC to inflamed tissue) as did LPS and thus the lack of upregulation of CD38 may be one important factor for spreading of *Borrelia*. To understand pathogenicity of *Borrelia* infections the group has developed an animal model for borrelial latancy treating the animals with ceftriaxone. This model will in the future be used to study spreading of the infection, determination of bacterial load, and to determine genetic alterations during the various stages of disease.

Programme objectives were successfully met with an additional theme introduced by collaboration with Professor Seppo Meri. Setting up of animal models was achieved, but further time (and funding) is required to exploit them fully. Research was multidisciplinary in that the three labs involved have different skills which were used to design a complementary approach (*Borrelia* genetics, genetic manipulation: animal models and in vivo studies: molecular aspects of innate immunity). Investigators were enthusiastic about the value of the MICMAN coordination in promoting dissemination of ideas and collaboration. A large number of papers has been published and submitted.

There was good organisation of meetings between collaborating laboratories. Three Ph.D. students have completed their studies. In addition to MICMAN meetings, the consortium has organized workshops and there have been several interlaboratory visits by members of the groups. Participation in MICMAN symposia was active. Of 14 publications 7 are results of the collaboration and out of 6 submitted manuscripts 4 are a result of the collaboration.

The collaboration saved a lot of time and money through exchange of expertise and reagents. The consortium leader attributes the valuable additional collaboration with Professor Meri to the MICMAN coordinator, and emphasises that the MICMAN symposia were beneficial for making contacts. MICMAN funding was critical for expensive activities of setting up animal models and microarray studies. Good media exposure, e.g. TV and radio interviews, was also attributed to MICMAN coordination.

The project identified potential vaccine candidates. Work on transmission via birds is of public health interest. The short time-frame of the MICMAN programme

makes progression to applications difficult. The consortium has excellent plans for future work on complement interactions, and a Sweden-Finland collaboration on sequencing the genome of one or more *Borrelia* species.

In conclusion this project represents a highly successful outcome from the MICMAN research program. The project identified potential vaccine candidates. Work on transmission via birds is of public health interest. The short time-frame of the MICMAN programme makes progression to applications difficult.

Project 3. EMERGENCE, SPREAD AND PERSISTENCE OF ANTIBIOTIC RESISTANCE IN NORMAL MICROFLORA

Charlotte Edlund, Professor, Karolinska Institutet, Sweden
Pentti Huovinen, Research Professor, National Public Health Institute, Turku, Finland.
In collaboration with:
Janet Jansson, Professor, Swedish University of Agricultural Sciences, Uppsala, Sweden,
Dan Andersson, Professor, Swedish Institute for Infectious Disease, Stockholm, Sweden,
Jari Javala, senior researcher, National Public Health Institute, Finland.

The consortium consisted of three Swedish and two Finnish research groups. The researchers are addressing a highly relevant topic concerning the role of antibiotic treatment on development of antibiotic resistance in different bacterial species of normal intestinal flora. To evaluate diversity, emergence of resistance and resistance genes in the intestinal microflora, 8 healthy volunteers divided into 2 groups were studied. One group received clindamycin 150 mg/day for 7 days, the other group received no antibiotics. Faecal samples were collected before and up to 24 months after initiation; samples were cultivated and single colonies typed and subjected to resistance analyses. The major findings were that changes were seen predominantly in the *Bacteroides* group, less in the *Enterobacteriaceae* and *Enterococcus* groups. Interestingly resistance in *Bacteroides* for clindamycin was detected for as long as two years. This resistance was frequently accompanied by other resistances, indicating presence of resistance genes in the faecal gene pool. Molecular typing and presence of resistance genes were also determined.

The different group members represent partly different competences ranging from environmental microbiology, molecular microbiology to clinical bacteriology. The scientific quality of the research is adequate although the very low numbers of study subjects and usage of only a single antibiotic will limit generalization of results derived from these studies.

The collaboration has consisted of analyses of different aspects of the clinical material in the different laboratories. There has also been transfer of technologies and repeated group meetings for exchange of ideas and results between the Swedish and Finnish groups. The outcome of the collaboration so far is relatively limited with one publication and four manuscripts in preparation. However, there have been additional publications from different consortium members since 2003 and there have been several presentations based on collaborative studies at different scientific meetings.

The investigators hope that the results from this consortium may lead to valuable information concerning choice of antibiotic therapy but as noted above, the limited scope of the project makes this outcome less likely.

The consortium has provided postgraduate training of five PhD students during the project period. There has also been exchange between the students in the form of five meetings involving the whole consortium at different locations during the project period.

In conclusion the outcome of the project so far is modest.

Project 4. PATHOGENS OF REACTIVE ARTHRITIS: RESEARCH OF ABNORMAL HOST-MICROBE INTERACTION

Kaisa Granfors, laboratory director, National Public Health Institute, Turku, Finland.

The interaction between an HLA-B27-expressing U937 monocytic cell line and *Salmonella enteritidis* was investigated in order to reveal the mechanism behind impared elimination of *Salmonella* in HLA-B27 positive U937 cells.

Interesting and novel work on the role of HLAB27 in reactive arthritis developing after *Yersinia* or *Salmonella* infection is reported. In this project, the group has collaborated with three international groups: R.Colbert, Cincinnati Children's Hospital, USA who provided several mutants of HLA-B27 with different misfolding characteristics; J.Hinton, Institute of Food Research, Norwich, UK, who made it possible to study *Salmonella* gene expression and S.Powis, Bute Medical School, University of St Andrews, Scotland, with whom the group studied the effect of cysteine mutations of HLA-B27. With these valuable collaborators, it was possible to make transfections of the U937 cell line and study *Salmonella* infection in U937 cells transfected with mutated and normal HLA-B27. Misfolded (mutant) HLA-B27 molecules provided an environment for intracellular *S. enteritidis* multiplication. In contrast, in cells where there was little or no misfolding the cells were able to resist *S. enteritidis* replication. Replication of *S. enteritidis* was shown to be controlled by p38 MAP kinase activity. Stimulation by LPS was shown to result in increased production of TNF-α and IL10. In cells with misfolded HLA-B27, regulation of TNF-α and IL10 was disrupted.

Two out of 5 publications and one review result from the MICMAN project. Five Ph.D. students have been involved in the study and one thesis has been defended. There was a one-month working visit to a UK lab and attendance at MICMAN symposia. MICMAN coordination provided valuable information on meetings and other topics of interest, and enhanced the profile of this research topic. In conclusion the project gave good value for the money spent.

Project 5. MICROBES AND ALLERGY: FROM POPULATION OBSERVATIONS TO ANIMAL MODELS AND PREVENTION PRODUCTS

Tari Haahtela, Professor, Helsinki University Central Hospital, Helsinki, Finland

The aim of this project was to determine the relation between microbial exposure and development of allergy. School children and their mothers have a 2.4 times and 4 times higher atopy frequency in Finland than in the neighbouring Karelia. Drinking

water in Karelia has on average 9-fold more microbial cells/ml. Regression analysis showed that high microbial cell content in drinking water was strongly associated with reduced risk of atopy. Finnish barn dust, as compared with urban home dust, had 5-fold higher cultivable bacterial content and a 40-fold higher total content of bacteria (by PCR). The bacterial diversity in barn dust was dramatically higher than that in home dust. In home dust, circa 90% of all the bacteria were of the genus *Bacillus* whereas in barn dust, Actinobacteria (*Streptomyces spp., Macrococcus spp. and Sphingomonas spp*) predominated. All major genera of the dust bacteria are devoid of endotoxin. There was therefore major difference in endotoxin content between barn and home dust. Barn dust elicited a far more vigorous inflammatory response in mice than home dust or PBS but these substantial immunological responses could hardly be related to endotoxin. Thus the impact of endotoxin as an environmental immunomodulator may have been overestimated.

This project which has its base at Helsinki University includes collaboration with researchers in Kuopio and Perth, Australia. The objectives are highly relevant and the approach of comparing the relation between dust and allergy in closely located high and low hygiene areas is sound. Scientific quality and innovativeness of the research is very good. The project activities have resulted in highly interesting concrete results that may have important implications for prevention of allergy and drug development. This research may lead to asthma prevention by the administration of probiotics. The project seems to be truly interdisciplinary with participation of a broad range of experts from preclinical as well as clinical disciplines. It has included annual training courses in allergology for clinicians, but limited postgraduate training. One student has received a PhD degree during the project period The project has resulted in an impressive number of publications emanating from the MICMAN support, including two in J.Allerg.Clin.Immunol. In addition the group presents a long publication list on related studies. According to the applicants, the MICMAN programme was considered very beneficial.

In conclusion this project represents a successful outcome from the MICMAN research programme with important data of practical importance that have also been reported in internationally well recognized journals.

Project 6. HOST-MICROBE CROSSTALK IN INFANCY: NUTRITION, ALLERGY, MUCOSAL IMMUNOLOGY AND INTESTINAL MICROBIOTA
Erika Isolauri, Professor, Turku University Central Hospital, Finland

The aim of this project was to study the role of probiotics in prevention of allergy in infants. Probiotics administered pre- and postnatally for 6 months to children reduced the prevalence of atopic eczema later in infancy and childhood to half (23 %) compared to the prevalence in infants receiving placebo (46 %), and the effect was shown to extend beyond infancy. The total numbers of IgM-, IgA- and IgG-secreting cells at 12 months were higher in infants breastfed and supplemented with probiotics as compared with breastfed infants receiving placebo. Faecal *Bifidobacterium* and *Lactobacillus/Enterococcus* counts were higher in breastfed than in formula-fed infants, and sCD14 in colostrum correlated with the numbers of IgM and IgA cells. In the long-term follow-up of the study population, the perinatal administration of probiotics appears to be safe. However, a trend was observed for weights to be lower

in the group receiving probiotics perinatally necessitating further examination of the long-term safety. In the long-term follow-up of the gut microbiota of the study cohort, the probiotic impact on gut microbiota succession was shown to be temporary, not interfering with the diversity of the microbiota later. Probiotics evidently act cooperatively with other nutritional compounds, such as polyunsaturated fatty acids which are assimilated by probiotics, and the immunological milieu in the gut.

This project which has its base in Turku has a true multidisciplinary approach with eleven different researchers/PhD students as well as some younger students. It also includes collaboration with a nutrition unit at Harvard. The project seems to be of high scientific quality addressing practically important aspects on the prevention of allergy in infants by the use of probiotics. The results of these studies may have practical implications for the design of suitable diets/formulas for allergy-prone (ectopic) children. Contacts have also been made with food industry for possible implementation of the findings from this project.

The project has included training of several post-graduate students who have had individual tutors. Students have also been invited to group meetings, young scientist training programs etc. The work of this project has resulted in seven publications in good journals and in addition the group has published frequently on related subjects during the project period. The main impact of the MICMAN support has been the funding, and seemingly no new collaborative constellations have been implemented.

In conclusion, the project is of good scientific quality and has resulted in useful results that probably could be commercialized. The results may end up in better asthma prevention by improving early nutrition.

Project 7. MICROBIAL FACTORS AND HOST RESPONSES DISCRIMINATING COMMENSALS FROM PATHOGENS

Ilkka Julkunen, Research Professor, National Public Health Institute, Finland
Timo Korhonen Professor, University of Helsinki, Finland.
With contributions from Professor **Seppo Meri** (University of Helsinki) and Professor **Riitta Lahesmaa** (University of Turku).

The project studied two pathogens (*Salmonella typhimurium* and *Streptococcus pyogenes*) and one non-pathogen, *Lactobacillus rhamnosus*, and their interactions with human macrophage and dendritic cells (DC). Pathogens gave a strong proinflammatory cytokine and chemokine response while the nonpathogen gave weak activation. Differences in responses between myeloid and plasmacytoid DCs were also reported. Surface proteases of *Yersinia pestis* and *Salmonella enterica* and other bacterial species were studied for their capacity to activate plasminogen or inactivate serpins. Factors, including surface carbohydrate structures which influence protease access to substrate were also characterised. These protease systems are likely to be important in bacterial spreading/dissemination. Further work was done in collaboration with Professor Meri on interaction with TLRs, and gene expression studies on monocyte-macrophage or DC differentiation have been initiated with Professor Lahesmaa.

The multidisciplinary nature of the project has mainly included construction of recombinant bacterial strains by the Korhonen's group and evaluation of their role in

host-parasite interactions, with a focus on initiation of inflammatory responses and innate immunity, by the Julkunen group. The scientific quality is high and the project has resulted in eight publications, most of which have been presented in very good internationally recognized journals. However, there has only been one joint publication. In addition there have been a number of other publications on related subjects from Julkunen's group and the project has resulted in several academic theses.

There were two working visits between collaborators' labs and several other international visits to other labs. It is not clear if these were funded by MICMAN. Three PhD and 2 MSc students were partially funded. One seminar and a lab course was organised with MICMAN. Annual meetings between the collaborating labs were also arranged. The value of MICMAN in promoting collaboration and dissemination of ideas was emphasized. The funding allowed more postgraduate students to be trained.

In conclusion, the research conducted within this project is scientifically of high quality and has resulted in several very good publications. However, the multidisciplinary nature of the project is still somewhat limited and it seems that the most important result of the MICMAN programme has been increased funding to an already strong research constellation. Research may be important in promoting use of probiotic bacteria in food. Discussions with food industry have been initiated.

Project 8. WHAT MAKES STAPHYLOCOCCUS AUREUS A PATHOGEN
Matti Karp, Professor, Tampere University of Technology, Finland,
Staffan Arvidson, Professor, Karolinska Institutet, Stockholm, Sweden

This is a consortium between five research groups (two Swedish and two Finnish and one from UK) studying pathogenic mechanisms of *Staphylococcus aureus*. The main theme of the project was to develop a type of biosensor to study regulation of virulence gene expression in *S .aureus*. A bacterial luciferase system was set up but was not sensitive enough. Technical improvements were made, and the system compared with PCR methods for monitoring expression. Lack of sensitivity of the assay delayed implementation of other aspects of the project, such as study of gene expression in *S. aureus* clinical isolates, and experimental infections in animals. Arvidson's lab investigated expression of a number of virulence genes by other methods, and in addition collected clinical material from 200 septicaemia patients for the study (with Skaraborg Hospital). They also collaborated with Stefan Karlsson (Skovde University) on mathematical modelling of virulence gene expression.

Karp moved from Turku to Tampere during the programme period which may have caused some delays in implementation. As noted above, assay development was slower than expected, so studies on clinical isolates and animal experiments are still to be completed. The project included technological method development by one partner, and expertise in virulence and clinical material from the other. Three papers have been published and another three (one joint) submitted. Due to personnel changes in both labs, exchange of ideas was not fully exploited.

The postgraduate training has been limited to training of young students. One student has visited the Swedish counterpart during one month. The value of the expertise of the Swedish collaborator in defining target virulence genes to study was emphasised by the Finnish researchers.

In conclusion this consortium has mainly focused on establishment of methods and formulation of study questions. The multidisciplinary approach is relatively modest and the outcome of the research has so far been relatively limited both with regard to student training and publications. This may partly be ascribed to the coordinator changing location from Turku to Tampere during the MICMAN programme period.

Project 9. HUMAN ENDOGENOUS RETROVIRUSES IN HEALTH AND DISEASE

Samuel Kaski, Professor, Helsinki University of Technology, Finland,
Jonas Blomberg, Professor, Uppsala University Hospital, Sweden.

New self-organizing map (SOM) -based methods for organizing, classifying and visualizing Human Endogenous RetroVirus (HERV) sequences were developed. New HERV groups, such as the ERV9-like, and epsilon-retrovirus-like ones, have been defined. This is of great interest as a basis for understanding not only HERV evolution and function but also the evolution and function of the human genome. A variant of Hidden Markov Models (HMM) was designed for detecting the beginning and end sequences of HERVs. Real-time PCR indicated that many HERVs are expressed at the RNA level, which is new. The involvement of HERVs in diseases like multiple sclerosis and schizophrenia was studied using PCR and no evidence for an increased expression was found. In the final stage of the research, new methods for inferring retrovirus expression from databases were developed.

There was good interdisciplinary potential: Kaski doing computation and data analysis and Blomberg doing clinical and lab studies. 3 papers have been published, and 2 submitted (2 are joint papers).

MICMAN coordination gave many opportunities to make contacts with researchers in different fields. The unbalanced funding in Sweden and Finland made the collaboration more difficult, as the Swedish partner was not funded. There were 5 working visits between collaborating labs, and 1 PhD student partially funded (to finish in 2007). This was a high-risk project and would not have been undertaken without specific funding from MICMAN.

In conclusion, the project was a good example of multi-disciplinary Finnish-Swedish collaboration and ended up with interesting results. It is good quality explorative and creative basic research.

Project 10. GENETIC SUSCEPTIBILITY TO STREPTOCOCCAL INFECTIONS

Juha Kere, Professor, Karolinska Institutet, Sweden and University of Helsinki, Finland
Jaana Vuopio-Varkila, Associate professor, National Public Health Institute, Helsinki, Finland
Jaana Syrjänen, Specialist in infectious diseases, Tampere University Hospital, Finland
Lennart Hammarström, Professor, Karolinska Institutet, Sweden.

Group A *Streptococcus* (GAS) is an important human pathogen, which causes a wide spectrum of diseases ranging from uncomplicated non-invasive infections to severe systemic infections. The aims of this very large project were to identify families with multiple cases of acute or recurrent erysipelas and with sepsis in order to identify predisposing genes and to improve our understanding of the underlying mechanisms that determine the severity of streptococcal infections.

In Finland, 427 patients with recurrent erysipelas have been identified and 52 families with two or more affected family members were found. To identify the disease locus, a genome scan was performed on 6 most informative families, using a SNP genotyping array. Positional candidate gene analysis is currently in process and a manuscript in preparation.Two consecutive serum samples at 1 month intervals were taken from 90 patients with acute erysipelas. The aim is to study the serological response against different streptococcal antigens and the possible association between serological response and the risk of recurrence.

In the Sepsis Study, 314 episodes of streptococcal septicaemia were studied.

The molecular typing of the isolates (emm typing and PFGE, when appropriate) from septicemia is currently underway. Beta-hemolytic streptococci were cultured from 328 throat swabs from probands and relatives of patients with recurrent erysipelas and from 253 throat and skin swabs from patients with acute erysipelas and their controls. The group A streptococci have been typed. The clonality of bacterial isolates will be studied by multilocus sequence typing and pulsed-field gel electrophoresis at the National Public Health Institute.

In Sweden, the family history of 380 patients with erysipelas infection was collected. Genetic screening is currently underway. Functional analyses revealed that the HLA class II haplotype of the individual determines the magnitude of superantigen-induced cytokine responses and consequently, the degree of systemic toxicity. The group also found a new mechanism by which the bacteria survive in spite of "adequate" antibiotic therapy by "hiding" within phagocytic cells.

The consortium had regular Finnish-Swedish meetings, but no joint publications yet. Contribution to researcher training and exchange is not mentioned in the reports. One paper by the Swedish group is in press at PLoS Medicine. One publication has been submitted by the researchers in Finland.

This study is very ambitious but addresses very important questions. An important finding at this stage of the project is the surprisingly high prevalence of familial erysipelas. This is a clinical problem which has hitherto been significantly underestimated. In addition, the potential finding of a gene associated with an isolated susceptibility to Streptococcal infection, adds significantly to our understanding of

the genetic background to specific ”holes” in the immune repertoire. These findings thus add to the growing understanding that the involvement of immunodeficiency in infectious diseases is much more common than hitherto realized.

In conclusion, the project is typically the kind of project a large programme like MICMAN should encourage. The GAS infections are so important that there is a strong need to increase our knowledge about this man-microbe interaction. Unfortunately, such a project cannot be completed in 3 years and no final results are available. However, the project is very well conducted and promising. It is likely that new and interesting observations will result from it.

Project 11. CYANOBACTERIA AND ACUTE HUMAN INTOXICATIONS
Liisa Lepistö, Professor, Finnish Environment Institute, Helsinki, Finland

The aim of this project was to determine the role of cyanobacteria and their toxins in environmental water samples for symptoms in humans. Over five hundred cyanobacterial water blooms were studied for species composition and the presence of toxins. Approximately 130 samples were associated with adverse human health effects. Over 150 patients were interviewed, and their symptoms were linked to the results of the water analyses. Such a wide research on acute human illness caused by cyanobacteria has not been conducted previously anywhere. The highly neurotoxic saxitoxin was found for the first time in Finland, and in high concentrations. Hepatotoxins were also found. The emerging cytotoxin cylindrospermopsin was detected for the first time from a boreal aquatic environment. The heterotrophic microbial diversity in association with cyanobacteria was shown to be extremely diverse. One new bacterial genus, *Paucibacter toxinivorans* that degrades cyanobacterial hepatotoxins was described. They were many Vibrios in the lakes but all non-O1, non-O139 serotypes. The potential fish pathogen *Aeromonas salmonicida* was identified from several cyanobacterial water blooms.

In conclusion the project has a good scientific quality and innovativeness and it contributed to the financing of one PhD student. Six publications in environmental journals and one in a journal of bacterial taxonomy (IJSEM) appeared. The project fits perfectly well in the programme and its outcome is very positive. This study is an example of a project that needs a large programme like MICMAN.

Project 12. MICROBIAL RESISTANCE TO INNATE IMMUNITY
Seppo Meri, Professor, Haartman Institute, University of Helsinki, Finland

Outstanding research on the interaction of complement proteins with microorganisms, which protects microorganisms from complement-mediated damage was presented. The researchers have analyzed the escape mechanisms of microorganisms and describe 5 different families of complement evasion molecules of Borrelia, Pneumococcus, GAS, GBS and Meningococcus) which protect from complement damage and 3 novel mechanisms by which this is achieved. Further work included determination of how mutants of factor H can lead to atypical haemolytic uraemic syndrome, and membranoproliferative glomerulonephritis type II. The mutations are mediated by reduced binding of factor H to cell surfaces, and to complement C3b/d and thereby the cells are not protected from complement attack.

Recent crystallisation and solution of structure of C-terminal of FH puts this lab in a world-leading position in a competitive field.

This group has collaborated extensively both with other MICMAN participants (Sven Bergstrom, University of Umeå, Sweden and Ilkka Julkunen National Public Health Institute, Finland) and Anna Blom, (University of Lund, Sweden) and with numerous groups in Finland (crystallography) USA, UK and Germany. The project has organised or participated in numerous training seminars and laboratory courses. In addition, it has had numerous inter-laboratory working visits. Four students received a Ph.D. and 1 student graduated from Helsinki Biomedical Graduate School. Many interesting results have been published from these studies. In total 10/23 papers are directly related to the project and 1/10 reviews/book chapters. Some findings may be developed into diagnostic tests and their findings will have implications for future drug and vaccine development. There has been real collaboration with many joint publications. There have been several short visits to and from Finland and joint meetings have been established. This project has been very successful but the time was too short.

The project leader is enthusiastic about the publicity value of the MICMAN programme. The project attributes a number of radio and newspaper interviews to publicity generated by MICMAN coordination. Funding allowed formation of a valuable new collaboration with Sweden (Bergstrom).

There is already some application of the results in diagnostics (Borreliosis and FH-related conditions), and others.

In conclusion the objectives of the MICMAN programme were in general well met in this project. Understanding and knowledge of the interaction between host and microbes and application of this knowledge to the maintenance of health and the prevention and treatment of diseases clearly was increased. Advantage of the technological and knowledge bases of the postgenomic era was taken, multidisciplinary networks were generated, researcher training and exchange was done, there were international contacts, and cooperation between universities and research institutes was strengthened. The practical applications of research findings were facilitated by the research findings. Without this programme, the most interesting part of the reported research may not have been possible. In the future the project will expand the complement aspect of research to cover other infectious diseases.

Project 13. DNA MICROARRAYS FOR STUDYING INTERACTIONS OF PROBIOTIC, PATHOGENIC AND NORMAL GUT MICROBIOTA BACTERIA WITH HUMAN INTESTINAL CELLS

Airi Palva, Professor, University of Helsinki, Finland

This project represents a non-consortium project at the Faculty of Veterinary Medicine in Helsinki. However, it includes close collaboration with the Finnish Microarray Centre and a university in the Netherlands. The focus of this project was to determine differential gene expression in tissue culture cells exposed to EHEC or nonpathogenic *E. coli*. The researchers first established a model for bacterial attachment to eukaryotic cells. In collaboration with the Finnish DNA Microarrray Centre hybridizations of eukaryotic RNA from cells with or without bacteria

attached were performed. Many genes were found to be up-regulated when bacteria were attached but the effect was generally not large. This study shows the difficulty with this technology and no publications or graduate student training has come out of this study. The group leader will now focus on transcriptional changes in bacteria.

The scientific quality of the project is difficult to evaluate, both because of lack of results and of publications from the project. However, it seems that the researchers are planning to partly abandon the use of micro-arrays and instead focus on alternative methodologies (e.g. real-time PCR).

A post doc got training abroad and established new collaborations. This part of the project resulted in some method transfer but no publications.

In conclusion, this is a small project with only two researchers directly involved. So far it has only resulted in establishment of new methodology that may be useful in future studies of related topics. The overall outcome of the project is difficult to evaluate since there are no publications yet and only limited training of younger researchers.

Project 14. HOST-MICROBE INTERACTIONS IN ACUTE AND PERSISTENT CHLAMYDIA PNEUMONIAE INFECTION

Mirja Puolakkainen, laboratory director, National Public Health Institute, Finland
Riitta Lahesmaa, Professor, Turku Centre for Biotechnology, Finland

Subproject Puolakkainen

This consortium consisted of three Finnish groups (Puolakkainen, chlamydiology, Vuola, experimental infection models and Lahesmaa, genomics, proteomics and immunological expertise). The focus of the consortium has been on unravelling the molecular biology of persistant chlamydial infections using both cell culture and mouse models. The consortium concentrated on three topics: transcriptomics using human respiratory tract cell cultures infected with *Chlamydia pneumoniae* to study transcriptional changes in the human cells with and without treatment with IFN-γ (persistence model) after infection. Candidate genes were identified. The second part was dealing with immunization of mice with naked Chlamydia DNA/SFV vector and elucidating resulting immune response and protection. Using DNA encoding MOMP, Omp2 and Hsp60 partial protection was obtained. In the third part CD8 T-cell epitopes were determined using transgenic HHD mice. Immunization with the secreted CopN was shown to give partial protection.

The consortium successfully collaborated, complementing each other's expertise. A longer programme would have been an advantage. Three of 10 publications are directly linked to the project, 4 of 5 submitted and 8 of 13 congress reports also are directly associated with the project. Six Ph.D. students participated the project.

Subproject Lahesmaa

This report expands on the work performed on transcriptomics and proteomics and the involvement of Professor Paavo Kinnunen's group, department of Bioinformatics, U. Helsinki, as well as the Finnish DNA Microarray Centre, the Bioinformatics Unit at CBT and CBT/VTT proteomics and Mass Spectrometry and their collaboration with Dr. Goodlett's group, Institute of Systems Biology, Seattle, USA. In addition to Puolakkainen's part this report includes further description of the transcriptional

analyses using the Affymetrix gene chip and software by which some novel differences in gene expression profiles were discovered. The second part described potential presence of chlamydial proteins in lipid raft fractions and their identification by mass spectrometry. The hope is to identify yet unidentified chlamydial proteins in this fraction that may explain how Chlamydia can survive in the intracellular environment.

One of 3 publications, 3 of 3 manuscripts, 3 of 3 congress reports and 1 Ph.D. thesis are the results of this part of the MICMAN project.

The consortium has obtained important new knowledge concerning the intracellular growth and the immune reactions to chlamydial infections in a mouse model. New approaches were made possible by participation in MICMAN. Increased understanding and knowledge of the interaction between host and microbes was obtained, and this knowledge was used to further exploit the immune reactions and immune targets that in the future may be used in the maintenance of health and the prevention and treatment of diseases. Clear advantage of the technological and knowledge based on the postgenomic era was taken, multidisciplinary networks were made, researcher training and exchange was promoted, international contacts were strengthened and cooperation between universities and research institutes was strengthened. The research findings may lead to practical applications at a later stage.

Thus, the project represents a good example of multidisciplinary approach with three different groups from different institutions in Finland representing partly different expertise in addressing host parasite interactions in Chlamydia pneumoniae infections. The project has a high scientific quality, and a very focused approach with clear objectives and goals. The consortium has obviously been beneficial for the excellent outcome of the project with several publications in good journals and in addition several submitted manuscripts with participation from the different groups of the consortium.

The consortium has also provided good postgraduate training with all together six PhD students involved with regular meetings throughout the project period. Two students have also defended their PhD thesis during the project period.

In conclusion, the MICMAN programme has obviously been very beneficial both financially but also in assisting in networking and in organizing meetings for consortium members. The consortium has also been successful in receiving continued grants from Academy of Finland and from the European Union. The results of the project may be useful for future vaccine development.

Project 15. MICROBIAL PATHOGENESIS OF CARDIOVASCULAR DISEASE
Pekka Saikku, Professor, University of Oulu, Finland

The focus of the project was detection of *Chlamydia pneumoniae* and markers of chronic *C. pneumoniae* infection in patient groups and in the discovery of gene polymorphisms related to either presence of *C. pneumoniae* or markers of a chronic *C. pneumoniae* infection. PCR sensitivity was tested and it was determined that only nested PCR has sufficient sensitivity. Patients with carotid artery disease, aortic aneurism and aortic occlusion were tested for presence of *C. pneumoniae* and good evidence was presented for high incidence of infection, and for association of infection with atherosclerotic diseases and for markers for chronic *C. pneumoniae*.

Using *C. pneumoniae* K7 infected mononuclear cells from patient buffy coat chlamydial inclusions were studied and genome copies were determined. Variation in inclusion production and genome copy numbers was found. To facilitate using K7 the genome has been sequenced. Polymorphisms in the host genes encoding IL6, TLR2, TLP4, LPB and ApoE were analyzed and compared to presence of disease. These studies are ongoing. The project resulted in a validation of data concerning determination of C. pneumoniae by PCR, detection of biomarkers for chronic C. pneumoniae infection and determination of gene polymorphisms and their relation to arteriosclerosis. Thus, there has been increased understanding and knowledge of the interaction between host and microbes.

Multidisciplinary networks were generated with cardiac surgery, cardiology, lipid biochemistry, genetics involved. Cooperation between universities and research institutes was facilitated. Collaboration between Finnish groups included those in the TEKES projects and from 2004 GEPARDI with Drug Discovery Centre and Inst. of Biotechnology, U. Helsinki and NPHI Oulu. Also involved were Clinical departments, industrial partners (Anilabsystem, Orion Diagnostica, Medix) and international collaborators T.Grayston, Seattle USA, and M.Maas U. Salzburg, Austria.

Two visits were made with the purpose of learning PCR technology and LPB genotyping. Seven of 22 publications 1 of 4 submitted papers, none of 5 book chapters and 3 of 4 PhD projects partially resulted from the MICMAN project. Two exchanges were made with a German collaborating laboratory.

The group leader had included industrial partners in the project and practical applications of research findings may later on be initiated. The project had good publicity on radio, television, partly attributable to MICMAN coordination. The project has assisted in setup of genomic/proteomic-based research to find anti-chlamydial drugs. The coordinator is retiring and the research will move to Helsinki.

In conclusion this project clearly benefited from participating in the MICMAN project.

5 Recommendations

The panel considers unanimously that the duration of three years for the programme is insufficient. First, a 3-year period favours short-term goals and hence selects for conservative and secure projects, at the expenses of innovation. Second, duration of three years is too short to allow a mid-term review, which is thought to be very useful. Hence, the panel recommends duration of 3 + 2 years or 3 + 3 years with a mid-term evaluation which could lead to the abandonment of the weakest or less collaborative projects.

The array of projects did not cover the whole field supposed to be covered by the name *"Microbes and Man"*. In particular, none of the main killer microbes was studied in the programme. Hence, the panel recommends the Academy to take the necessary action to promote virology, parasitology and cellular microbiology in Finland and also, to pay more attention to global health problems.

The panel recommends an increase in the mobility of young researchers (PhD and post-docs). More advantage should be taken from the enormous potential of the consortia to exchange researchers and make them familiar with more facets of infection biology. One way to achieve this goal would be to promote the recruitment of post-docs rather than PhD students, with the funding of the programmes. Hiring post-docs is the best way to distribute and spread scientific know-how among the different laboratories within a country. These post-docs may be recruited among the students finishing their PhD in other laboratories from the same programme. This change in the recruitment policy would also improve the career prospects of the PhD students.

The panel was struck by the feeling of insecurity that was apparent among PhD students. The panel considers that the funding of PhD students should, in any case, be secured for four years. The end of a research programme should not lead to the arrest or reorientation of a PhD project funded by the programme. It is, in general, the duty of the supervisor and the university to secure funding for the whole period of a PhD that has been started. The panel would also like to recommend that PhD students are coached to help them identifying the opportunities for a scientific career in academia or industry. This coaching would help PhD students to position themselves in society and would help them to make career choices and envision their future with optimism.

Concerning education, the panel suggests that some consortia should be invited to organize graduate courses open to all the students of the programme. In a more general view, the panel would recommend the building of graduate schools or organisation of PhD courses around national research programmes.

The panel recommends that the Academy facilitates the continuation of the most fruitful collaborations that emerged from MICMAN. This continuation should certainly not apply to the whole programme and could take different forms, but the present abrupt end of the programme appears to the panel as a potential waste of resources. New related programs could for example be created around the following themes: innate immunity and inflammation; chronic infections and commensalism, system biology of infection.

The panel recommends stronger promotion of international collaborations. It also recommends recruitment of international researchers to the programs in Finland and Sweden.

Appendix 1.
Projects, project leaders and funding of the projects

1. Bacterial:Epithelial cross-talk and the establishment of the mucosal immune system

Agace William, University of Lund, Sweden, 171 000 Eur
Svanborg Catharina, University of Lund, Sweden, 40 000 Eur
Wick Mary-Jo, University of Göteborg, Sweden, 139 000 Eur
Jalkanen Sirpa, University of Turku, Finland, 140 580 Eur
Skurnik Mikael, University of Helsinki, Finland, 162 870 Eur

2. Reactivation and immune evasion of Borrelia infection

Bergström Sven, University of Umeå, Sweden, 350 000 Eur
Viljanen Matti, University of Turku, Finland, 300 000 Eur

3. Microbial ecology of man in health and disease: Emergence, spread and persistence of antibiotic resistance in the normal microflora

Edlund Charlotta, Karolinska Institutet, Sweden, 350 000 Eur
Huovinen Pentti, National Public Health Institute, Finland, 260 580 Eur

4. Pathogenesis of reactive arthritis: Research of abnormal host-microbe interaction

Granfors Kaisa, National Public Health Institute, Finland, 50 000 Eur

5. Microbes and allergy: from population observations to animal models and prevention products

Haahtela Tari, University of Helsinki, Finland, 167 400 Eur

6. Host-microbe crosstalk in infancy: creating a balance between the internal and external environments

Isolauri Erika, University of Turku, Finland, 167 400 Eur

7. Microbial factors and host responses discriminating commensals from pathogens

Julkunen Ilkka, National Public Health Institute, Finland, 250 000 Eur
Korhonen Timo, University of Helsinki, Finland, 250 000 Eur

8. A paradox of a microbe and man - what makes Staphylococcus aureus a pathogen?

Karp Matti, Tampere Technical University, Finland, 150 000 Eur
Arvidson Staffan, Karolinska Institutet, Sweden, 100 000 Eur

9. Infectious origins of the human genome Human endogenous retroviruses in health and disease

Kaski Samuel, Helsinki University of Technology, Finland, 180 000 Eur

10. Genetic susceptibility to streptococcal infections

Kere Juha, Karolinska Institutet, University of Helsinki, Finland, 181 730 Eur
Vuopio-Varkila Jaana, National Public Health Institute, Finland, 160 000 Eur
Syrjänen Jaana, University of Tampere, Finland, 113 600 Eur
Hammarström Lennart, Karolinska Institutet, Sweden, 180 000 Eur

11. Cyanobacteria and adjacent microbes: causes of acute human intoxications and indicators of water quality

Lepistö Liisa, Finnish Environment Institute, Finland, 180 000 Eur

12. Microbial resistance to innate immunity

Meri Seppo, University of Helsinki, Finland, 200 000 Eur

13. DNA microarrays for studying interactions of probiotic, pathogenic and normal gut microbiota bacteria with human intestinal epithelial cells

Palva Airi, University of Helsinki, Finland, 200 000 Eur

14. Host-microbe interaction in acute and persistent Chlamydia pneumoniae infection

Puolakkainen Mirja, National Public Health Institute, Finland, 150 000 Eur
Lahesmaa Riitta, University of Turku, Finland, 150 000 Eur

15. Microbial pathogenesis of cardiovascular disease

Saikku Pekka, University of Oulu, Finland, 250 000 Eur

Appendix 2. The Steering Programme Committee

MICMAN, Microbes and Man research programme

(2002-2003)
Academy of Finland:
- Professor Marja Makarow, Research Council for Health, (chairperson)
- Professor Annele Hatakka, Research Council for Biosciences and Environment (vice chairperson)
- Professor Timo Vesikari, Research Council for Health
- Professor Juha Sihvola, Research Council for Culture and Society

Swedish Foundation for Strategic Research:
- Dr. Olle Edqvist, Swedish Foundation for Strategic Research
- Dr. Henryk Wos, Swedish Foundation for Strategic Research
- Professor Olle Stendahl, Linköping University
- Professor Hans Wolf-Watz, Umeå University

An additional expert:
- Academician, professor Pirjo H. Mäkelä, National Public Health Institute

(2004-2006)
Academy of Finland:
- Professor Marja Makarow, University of Helsinki (chairperson)
- Professor Timo Vesikari, Research Council for Health (vice chair)
- Professor Marja-Liisa Hänninen, Research Council for Health
- Professor Tiina Mattila-Sandholm, Research Council for Biosciences and Environment

Swedish Foundation for Strategic Research:
- Dr. Henryk Wos, Swedish Foundation for Strategic Research
- Professor Olle Stendahl, Linköping University
- Professor Hans Wolf-Watz, Umeå University

An additional expert:
- Academician, professor Pirjo H. Mäkelä, National Public Health Institute

Also participating in the meetings of the Steering Programme Committee:
- Dr. Soile Juuti, programme manager, Microbes and Man research programme
- Dr. Sirpa Nuotio, programme manager, Academy of Finland, Programme Unit
- Dr. Tuula Aarnio, programme manager, Academy of Finland, Programme Unit

Appendix 3. Self-evaluation form for the projects

MICMAN, Microbes and Man research programme
Years 2003-2005

A. Description of the project

Project title (and home page, if applicable):
Consortium (YES/NO):
The group leader (Name, position and organisation):

1) A) The national and international collaboration and networking of the project.

*Free text describing your cooperation. Please, **specify Finnish-Swedish cooperation within MICMAN**, collaboration with industry, clinical settings and collaboration between universities and research institutes. Specify if the networking have resulted in co-publication or other documented output.*

B) National or international visits

(duration of one week or more) (COPY THIS SECTION WHEN NEEDED)

Type of visit (visiting researcher, teacher, etc):
Aim of the visit:
Host:
Time:
Participant(s) from the project:

2) Multidisciplinarity of the project

How did multidisciplinarity become concrete?
(A multidisciplinary project involves researchers from two or more disciplines where all researchers address a problem from their disciplinary perspective respectively. The outcome of the project is the added knowledge that is gained by incorporating several disciplinary perspectives.)

3) The post graduate training of the personnel

How the training in the project was organised in general? What training did the researchers receive and who organised it? Describe the most significant contribution to graduate education.

4) The main results of the project

(This section will be published at the MICMAN homepage: www.aka.fi/micman.)
Please describe the main scientific results and achievements (including the innovativeness (novelty) in comparison to other research in your field). Max. length for single (non-consortium) projects: 2 pages. Max. length for consortia projects: 3-4 pages. (The projects of a consortium may present a) a joint text or b) a joint short summary + own texts of each group.)

TITLE OF THE PROJECT
Project leader: (Name, organization, contact address, telephone number and e-mail): Researchers: (A list of researchers working in this project (name, organization). (Hint: Copy and update the information of your project presented at the MICMAN web-pages: www.aka.fi/micman <Projects)

B. Self-evaluation of the project

The applicability of the research results - contribution to practice and decision making.

1) How could your results be utilized and by whom?

2) When do you think your results could start showing impact?

3) What would be the best long-term impact indicators of your results?

4) How do your results contribute to the competitiveness of your country?

Communication of the results.

5) How did/does the project communicate with the end users?

6) Has your research results of the MICMAN-project been presented or published in any media outside the scientific community? If yes, what media and when? Who initiated the publicity?

Objectives of the MICMAN.

The objectives of the MICMAN were:

- *to increase our understanding and knowledge of the interaction between host and microbes*
- *to apply this knowledge to the maintenance of health and the prevention and treatment of diseases*
- *to take advantage of the technological and knowledge bases of the postgenomic era*
- *to generate multidisciplinary networks*
- *to promote researcher training and exchange*
- *to promote international contacts*
- *to strengthen cooperation between universities and research institutes*
- *to facilitate the practical applications of research findings*

7) How did the MICMAN programme work as a whole compared to the objectives set for it? It was

☐ Excellent ☐ Good ☐ Fair ☐ Poor

8) Were the objectives relevant and achievable? General discussion on the objectives and how they were met.

9) How did the Finnish-Swedish collaboration succeed? What was good and what could have been better?

Coordination and programme administration.

10) How did the coordination manage its task in trying to achieve the objectives? It was

☐ Excellent ☐ Good ☐ Fair ☐ Poor

11) How did your project benefit from the coordination? Did it create any collaboration beyond your own group?

12) Which of the arranged events did you find useful and why?
(MICMAN events are listed at www.aka.fi/micman <Events)

13) What kind of support would your project have required more from the coordination? What did the coordination fail to achieve?

Project funding.

14) How essential was the MICMAN funding for your research?
☐ Very essential ☐ Essential ☐ Not very essential ☐ Not at all

15) How the MICMAN funding has affected the type of academic position you have today?

16) Other effects of the funding (positive/negative)?

17) Was the funding sufficient compared to the research plan?
☐ Yes ☐ No

18) What kind of any added value has the research field gained for having a programme compared to normal research grants? What about your project?

19) How the programme has enhanced the development of the research area?

20) What kind of added value has the Finnish-Swedish funding collaboration produced?

21) How beneficial the participation in the MICMAN programme has been to your research if NOT considering the direct funding?
☐ Very beneficial ☐ Beneficial ☐ Not very beneficial

22) What did you achieved or arranged that could not have been done without the MICMAN funding?

Future

23) What are the future possibilities and plans of the team after MICMAN?
(On terms of funding, completion of studies, employment of the personnel, etc.).

24) What are the most important future topics of this research area?

25) Other comments

Appendices:

1. A LIST OF PUBLICATIONS

A full list of publications and other outcomes of the project (include ONLY the years 2003-2006).
Underline those publications and other outcomes arising from this research funding, i.e. bearing an indication of funding granted by the Academy of Finland or the Swedish Foundation for Strategic Research for this project!

Articles (use the following classifications OR the classification in the research report of the Academy of Finland:
1. Scientific articles (reviewed)
2. Other scientific articles
3. Popular articles
4. Submitted manuscripts (indicate status: submitted/accepted/in press).
(Abstracts and manuscripts in preparation are not reported)

Scientific reports
Books or book chapters
Academic theses
Patents
Television and radio programmes
Scientific awards
Other professional documented activities

2. **An electronic version of max. three most important publications arising from the MICMAN research funding.**

Appendix 4.
Material for the evaluation

MICMAN, Microbes and Man research programme

0	BACKGROUND MATERIAL
	Finland:
	Research in Finland (2005)
	Scientific Research in Finland
	Research Funding and Expertise (Academy of Finland)
	Annual Report 2005 (Academy of Finland)
	International Strategy (Academy of Finland)
	Research Programme Strategy (Academy of Finland)
	Academy of Finland Research Programmes
	Evaluation Reports (Academy of Finland): examples
	Sweden:
	Swedish Foundation For Strategic Research: Activity report 2004
	Swedish Foundation For Strategic Research: Research that shapes our future (2004)
1	INTRODUCTORY MATERIAL
	GUIDELINES FOR THE EVALUATION
	EVALUATION PLAN
	AGREENMENT ON SCIENTIFIC COOPERATION BETWEEN THE AF AND THE SSF
2	PLANNING AND LAUNCHING OF THE RESEARCH PROGRAMME
	MEMORANDUM (= CALL TEXT)
	SUMMARY OF THE PROPOSALS SUBMITTED TO THE CALL
	RESEARCH PLANS OF THE PROPOSALS
	EVALUATION RESULTS OF THE PROPOSALS
	FUNDING DECISIONS - APPLIED/GAINED FUNDING
3	IMPLEMENTATION OF THE RESEARCH PROGRAMME
	BROCHURE
	MICMAN WEB-PAGES
	MICMAN-EVENTS
	MEDIA RELEASES
	MICMAN-NEWS
	MICMAN SUPPORT FOR SHORT-TERM GRADUATE EXCHANGE BETWEEN LABORATORIES
	PROPOSAL FOR A GRADUATE SCHOOL IN INFECTION BIOLOGY
	STEERING PROGRAMME COMMITTEE MEETING MINUTES
4	RESULTS OF THE RESEARCH PROGRAMME
	PUBLICATIONS AND DEGREES
	COMPILATION OF THE PROJECT ABSTRACTS (years 2003, 2005, 2006)
	SELF-EVALUATIONS OF EACH PROJECT
	PUBLICATIONS (n = 0-3) OF EACH PROJECT
	FINAL REPORT FORMS OF EACH PROJECT
	SUMMARY OF THE SELF-EVALUATIONS OF THE PROJECTS
	COORDINATION REPORT

Appendix 5.
The agenda of the evaluation panel meeting

MICMAN EVALUATION PANEL MEETING

Time: 17-18 October 2006
Place: Room 564, (5th floor), Academy of Finland, Vilhovuorenkatu 6, Helsinki

16 October 2006 (Monday)

Evening	Arrival in Helsinki

17 October 2006 (Tuesday)

9:30–10:00	Presentation of the participants; agenda; working methods
10:00-10:15	"Research programme evaluation: objectives and instructions", Programme manager Sirpa Nuotio, Academy of Finland
10:15–10:35	"Microbes and Man research programme and its coordination" Programme manager Soile Juuti, MICMAN
10:35–10:50	Interview with the programme manager Soile Juuti
10:50–11:00	Break
11:00–11:30	Project presentations (done by the panel members)
11:30–12:00	Interview with Res.Prof. Pentti Huovinen, National Public Health Institute
12:00–13:00	Lunch
13:00–14:45	Project presentations ...continues
14:45–15:00	Break
15:00–15:30	Interview with Prof. Seppo Meri, University of Helsinki and Doc. Mirja Puolakkainen, National Public Health Institute
15:30–16:10	Interview with PhD students (Merja Oja, Tech.Univ.Helsinki; Taina Lajunen, National Public Health Institute; Taija Pietilä, National Public Health Institute, Pauliina Hartiala, Univ.Turku)
16:10–17:15	Project presentations ...continues
17:15	Transportation to the hotel
19:00	Dinner together with the Steering programme Committee of MICMAN

18 October 2006 (Wednesday)

8:45–9:00	Summary of the first day
9:00–9:30	Interview with Prof. Sven Bergström, University of Umeå, Sweden (by phone)
9:40-10:15	Interview with Res.prof. Ilkka Julkunen National Public Health Institute, Prof. Mikael Skurnik, University of Helsinki, and Ass.prof. Jaana Vuopio-Varkila National Public Health Institute
10:15-12:00	Drafting of report
12:00-13:00	Lunch
13:00-16:30	Drafting of report.
16:30	Transportation to the airport

The Microbes and Man research programme (MICMAN) was launched by the Academy of Finland and the Swedish Foundation for Strategic Research in 2002 and implemented during 2003-2005. The specific objective of the MICMAN programme was to increase our understanding and knowledge of the interaction between host and microbes, and to apply this knowledge to the maintenance of health and to prevention and treatment of diseases.

This report is the evaluation report on the MICMAN programme by an international expert panel. The report includes the assessment of the programme as well as recommendations for future.

ACADEMY OF FINLAND

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