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EU-funded FP6 Research projects on Antimicrobial Drug Resistance
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INTRODUCTION

COMBATING ANTIMICROBIAL DRUG RESISTANCE

The discovery and use of antibiotics has had an enormous impact on our healthcare system. Nowadays, the treatment and prevention of microbial infections fully depends on the availability of effective antibiotics. In addition to this, advanced surgical procedures like organ transplants, cancer chemotherapy and care of preterm babies heavily rely on effective antibiotics. Unfortunately, the emergence of and rise in resistance to the currently available antimicrobial drugs threatens the treatment of both hospital- and community-acquired bacterial infections and endangers many modern medical practices. This situation is further aggravated by a sharp decline in the discovery of new antimicrobial drugs needed to overcome drug resistance. Such developments represent a looming crisis for our healthcare system.

It is crucial to contain antimicrobial drug resistance (AMDR) and to nourish research aimed at combating it. This research need has been addressed within the EU framework programmes where AMDR has been given a high priority over the last decade with significant financial support from the Health Directorate of the Directorate-General for Research (DG RTD) in the European Commission.

The development and spread of AMDR are amongst the areas that are currently being investigated together with novel evidence-based approaches to managing patients with a view to optimising antibiotic use.
In addition, the discovery and development of novel antimicrobial drugs and the identification of their molecular targets are areas that have attracted funding. This is of prime importance since only few antimicrobial agents have been launched during the last 30 to 40 years. Under-investment in antibiotic research and development by the pharmaceutical industry has contributed to this problem. The research projects that are supported by the Health Directorate of DG RTD aim to form and support multidisciplinary collaborations, obtain a critical mass of researchers investigating AMDR within Europe and mobilise the European biotech industry.

The project catalogue contains information about AMDR projects funded under the Sixth Framework Programme (FP6). It provides an overview of the scientific challenges, the research goals addressed and the expected outcome of projects. The information presented also shows the involvement and participation of a multitude of small and medium-sized enterprises (SMEs) working in close collaboration with the academic institutions. The concerted efforts of the research consortia will most likely result in significant advances in three distinct areas. Firstly, a more appropriate use of currently available antibiotics is aimed at in order for these drugs to remain effective as long as possible. Secondly, an increase of our current knowledge of the biological processes that underlie AMDR will result from several projects that have received funding. Within such projects attention is also being paid to the transfer of resistance as well as the biological costs (fitness costs) of resistance. The third area concerns the development of novel antimicrobial drugs that will benefit from research projects that aim to identify compounds capable of inhibiting processes that are essential for bacterial growth or projects explore natural resources to obtain new antimicrobials.

Under FP6, the total EC contribution committed to discovery and translational research activities for projects that specifically focus on AMDR or on certain aspects of AMDR is more than EUR 160 million. In addition, several closely related projects funded by the Directorate-General for Health and Consumer Protection (SANCO) are also included for a comprehensive overview of the scope of Community funding in this field. However, although vaccination may have a significant impact on reduced use of antibiotics, no vaccine research projects have been included in this compilation.

Research projects in this catalogue are of prime importance since this type of research is essential for a continuation of the effective control of bacterial infections that is required to sustain our current high level of medical care as well as public trust in our healthcare system.
BACKGROUND

The ABS INTERNATIONAL project sought to further develop organisational competencies regarding adequate antibiotic use in the cooperating hospitals of the partner countries, as well the qualification of doctors and pharmacists in adequate antibiotic use. Through eight Work Packages (WPs), the project developed and validated quality indicators and process measures for antibiotic use.

Problem:

In human medicine, the use of antibacterial agents for the treatment of viral infections and the unjustified use of substances with an extremely broad activity spectrum are regarded as the main causes (among others) of the resistance problem.

AIMS

The general objectives of the project were:

- to develop organisational tools and qualified capacities for identifying and distributing best practice on the prudent use of antimicrobial agents in human medicine in hospitals;
- to enhance and implement specific strategies for the prudent use of antimicrobial agents in hospitals;
- to elaborate methods for evaluating the applied antimicrobial strategies;
- to disseminate project results.

EU Project:

ABS International

1.1 Project Management
1.2 Dissemination of Results
1.3 Evaluation of the Project
1.4 Planning and Preparation
1.5 Process Measures/QI for AB Use
1.6 Preparation per Partner Country
1.7 Implementation per Partner Country
1.8 Preparation of the postproject phase

- Project number: 2005208
- EC contribution: €798,598
- Duration: 24 months
- Starting date: 1 September 2006
The main deliverables of the project include:

- standards for ABS Tools;
- ABS training and ABS consulting for cooperating hospitals;
- country reports on the results of the ABS maturity survey;
- ‘Guidelines to Further Develop and Define Antibiotic Use in Hospitals’;
- ABS expert network.

ABS INTERNATIONAL is further developing the strategy for the prudent use of antimicrobial agents in hospitals and for the distribution of best practice including training among 9 countries of the European Union, 4 of which are new Member States.

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Background

Genetic population analyses of Enterococcus faecium revealed the presence of a High-Risk Enterococcal Clonal Complex (HiRECC) resistant to multiple antibiotics and responsible for most nosocomial VRE (vancomycin-resistant E. faecium and Enterococcus faecalis) infections and hospital outbreaks worldwide. In ACE, the evolutionary development of HiRECC in E. faecium and E. faecalis will be further unraveled and combined with new knowledge on intra- and inter-species gene transfer, and biological fitness costs of hospital adaptation.

Problem:
Nosocomial VRE infections are rising in Europe, with proportions of more than 10% among enterococcal bloodstream infections in 9 countries in 2005 (Fig. 1).

Aims
The main project objectives include:

■ determining the population structure of enterococci and the evolutionary development of HiRECC;
■ improving understanding of the biological fitness costs of hospital adaptation of Enterococci.

Expected results
The results ACE expects include:

■ a typing scheme for resistant plasmids to construct a catalogue of resistance determinants, transposons, and plasmids present in different host groups.

Potential applications:
ACE is expected to contribute to new strategies that will reduce the spread of resistance and infections, and create an opportunity to develop vaccination which could prevent infection and colonisation, respectively, with multi-resistant HiRECC.

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Project number: LSHE-CT-2007-037410 ■ EC contribution: €3 148 000 ■ Duration: 36 months ■ Type: Specific Targeted Research Project ■ Starting date: 1 February 2007
Figure 1. Proportion vancomycin non-susceptible enterococcal blood isolates, EARSS 2005 (www.earss.rivm.nl).
BACKGROUND
The ACE-ART project aimed to provide a critical evaluation of the impact on non-pathogenic bacteria of antibiotic use in agriculture, and in the prophylaxis and treatment of disease in humans. The consortium established collaboration with the Joint Action Team of the International Organization for Standardization (ISO) and the International Dairy Federation (FIL/IDF).

A total of four Work Packages (WPs) focused on the development of standardised phenotypic procedures, the validation of model systems for gene transfer evaluation, the genetic basis of the detected resistances and transmission mechanisms, and the dissemination of project results.

Problem:
The emergence and evolution of antibiotic resistance in bacteria represents a major financial and societal cost. Despite concern that the use of antibiotics in the food chain contributes to the development of resistant bacteria, research has yet to provide the data necessary for the development of an effective risk management strategy. Risk assessment of antibiotic resistant, non-pathogenic bacteria present in the food chain requires data on the sources of these bacteria, their genetic composition and potential for resistance transfer. The assessment of drug resistance is a mandatory requirement in the approval process of EFSA for bacterial feed additives and plant protecting agents.

AIMS
ACE-ART aimed to provide a critical evaluation of the role of antibiotic use in agriculture, and in the prophylaxis and treatment of disease in humans. Unlike other studies, focused on pathogens, this project is focused on non-pathogenic bacteria. Strains belonging to Lactobacillus, Bifidobacterium, Lactococcus and Streptococcus thermophilus have been used as they can be found in a wide range of habitats. Moreover, they are industrially important bacteria, used as starter cultures for fermented food. Within this project the importance of these bacteria as a source of antibiotic resistance genes (Work package 1) will be assessed. The project will also examine the transmission of resistance in the environment and in the animal and human gut (WP 2) and establish the genetic basis of the detected resistances and transmission mechanisms (WP 3). Dissemination of results and links with consumers’ organization will be provided by WP4; an industrial platform will assure the link with 14 industries producing starter cultures. This research will sought to establish a dataset on the occurrence and transmission of antibiotic resistance, providing the scientific basis for an antibiotic application strategy to inhibit the further development of resistance in pathogenic bacteria.

Project number: CT-2003- 506214  EC contribution: €2 462 000
Duration: 36 months (+6 of extension)  Type: Specific Targeted Research Project
Starting date: 1 January 2004
OBTAINED RESULTS
A phenotypic procedure to evaluate the drug resistance profile of food bacteria was developed; this procedure is now the ISO method. New MIC were provided to the European Food Safety Authority (EFSA) for safety evaluation of these bacteria; data provided by ACE-ART has been used to update the guidelines for bacterial safety evaluation. This achievement is significant, as this support to EU policy was a project objective.

Potential applications:
Methodology developed by ACE-ART and MIC can be used by the industry in the process for developing new starter or probiotic bacteria.

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INTEGRATING GENOMICS-BASED APPLICATIONS TO EXPLOIT ACTINOMYCETES AS A RESOURCE FOR NEW ANTIBIOTICS

http://www.swan.ac.uk/research/ActinoGEN/

BACKGROUND
ActinoGEN is an Integrated Project aimed at developing novel genomics-based approaches to exploit hitherto overlooked genetic resources for new antibiotics. To greatly accelerate the drug discovery process, a parallel strategy will be to engineer generic hosts optimised to produce high antibiotic yields. With the complete genome sequence of the model actinomycete, Streptomyces coelicolor, and mobilisation of a pan-European effort to apply newly developed multidisciplinary post-genomic technologies, a holistic understanding of the physiology and regulation of antibiotic biosynthesis is achievable for the first time. This will, in turn, permit rational intervention to engineer generic hosts for high-yield antibiotic production. This synergy of discovery linked to overproduction will place the European biotechnology sector at the forefront of developing much-needed new antibiotics to combat multi-drug resistant pathogens.

Problem:
Multiple drug-resistant bacteria are a major threat to human health and a significant burden on already stretched medical budgets. This threat is predicted to increase in severity. Of major concern are antibiotic-resistant nosocomial infections.

AIMS
The aim of ActinoGEN is to combine new functional genomic technologies with chemical analysis in an integrated multidisciplinary approach. ActinoGEN proposes three parallel objectives to discover and develop new antibiotics based on exploiting the genetic resources of actinomycetes:

1. activate cryptic antibiotic biosynthetic pathways;
2. rely on the discovery of new antibiotic biosynthetic pathways from diverse actinomycetes;
3. follow through on combining biosynthetic pathways to direct synthesis of new antimicrobials.

EXPECTED RESULTS
ActinoGEN expects to achieve the following results, among others:

1. establishment of generic procedures for the activation of cryptic antibiotic biosynthetic pathways;
2. expression of a variety of heterologous cryptic pathways after their transfer to defined superhost antibiotic production strains;
3. establishment of refined genomic-based procedures for analysis of metagenomes to identify new antibiotic biosynthetic pathways;
4. optimised expression of new combinatorial antibiotics, together with structural analysis and antimicrobial spectra;
5. generic antibiotic production superhosts derived by rational genomics-driven manipulation of S. coelicolor;
6. refined superhost strains optimised for production of key new antimicrobials.

Project number: LSHM-CT-2004-005224  EC contribution: €9 384 133
Duration: 60 months  Type: Integrated Project  Starting date: 1 January 2005
Potential applications:
The development of new technologies for antibiotic discovery and production will benefit European small and medium-sized enterprises (SMEs) in the biotechnology sector. Application of these new genomics-based procedures and technologies for discovery and exploitation of natural products can provide a platform for a renaissance in drug discovery after 15 years of stagnation. New antimicrobials discovered in the course of the project can potentially help alleviate the current crisis in treatment of multiple drug-resistant pathogens.

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BACKGROUND
AMIS sought to use the strength of the innate immune system to design antimicrobial drugs for future generations. Antimicrobial proteins are often combined with inflammatory signals in one single molecule. AMIS took that same approach and reshuffled different parts of different molecules to make novel effector molecules that still have these combined functions but are optimally adapted for therapeutic intervention. The consortium selected the most promising and innovative compounds with this dual mode of action.

Problem:
The success with which antibiotics have been used to combat infectious diseases is under serious threat from the increasing development of antimicrobial resistance. To fight infectious diseases effectively, we have to broaden the approaches in therapeutic intervention.

AIMS
Activators, receptors, effectors and inhibitors are an integral part of the complex mechanism of interaction in the innate immune system, combining cellular stimulation and anti-microbial action. These interaction mechanisms formed the core focus of AMIS.

EXPECTED RESULTS
The partners expect to make an array of fusion proteins that combine strong antimicrobial with inflammatory signals so that these two actions work in concert. Furthermore, the consortium will investigate how the innate immune system can effectively recognise and kill a bacterium without developing major resistance.

Potential applications:
The collaborative research will lead to proof-of-principle for a novel treatment approach to address antimicrobial resistance by combining the innate immuno-stimulation with the antimicrobial capacity of naturally occurring substances of the human innate immune system.

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The ANTIBIOTARGET project will establish an innovative research-driven training programme in state-of-the-art technologies in the fields of molecular bacterial pathogenicity, functional genomics and biological chemistry directed towards the development of novel antibacterial therapies which combat the disease-causing and natural antibiotic resistance capacity of pathogenic bacteria.

Problem:
Infectious diseases account for more than 13 million deaths a year (one in two deaths in developing countries) and are the main causes of mortality and morbidity around the world. Increasing human mobility and changing social patterns as well as the increasing number of immunocompromised individuals as a result of ageing populations, AIDs and advances in surgery and cancer chemotherapy, have all increased the spread and risk of infection. Furthermore, the WHO has stated that “no population is more vulnerable to multi-drug resistance than those admitted to hospital wards”. Consequently, the spread of antibiotic resistant bacteria in hospitals means that medical procedures once previously taken for granted may have to be abandoned with enormous impacts on morbidity and mortality.

The emergence of multi-antibiotic resistant bacteria and the failure of drug discovery programmes over the last 10 years to provide new broad-spectrum antibiotics with novel modes of action is a major threat to public health worldwide.

AIMS
The research project will focus on Pseudomonas aeruginosa as a model pathogen since it is an important, intrinsically resistant Gram negative bacterium responsible for high infection rates in humans within the hospital environment, has a completely sequenced genome, is highly amenable to genetic manipulation and the ANTIBIOTARGET partners are all recognized international research leaders in the molecular biology, biochemistry, genetics and pathogenicity of Pseudomonas. In addition, the ubiquitiness of this organism would make any new discoveries potentially applicable to other nosocomial pathogens. Given the major threat to human health posed by multi-antibiotic resistance, the strategies used in this project will offer not only a timely opportunity to discover new antibacterial targets but also to provide a pool of highly skilled scientists with specific expertise directed towards the discovery of novel anti-infective agents.

ANTIBIOTARGET will identify targets involved in promoting or regulating attachment, the biofilm lifestyle, virulence, and intrinsic antibiotic resistance, and will develop strategies for discovering new agents that inhibit the ability of bacteria to colonise tissues, cause disease and resist conventional antibiotics.

- **Project number:** MEST-CT-2005-020278  
  - **EC contribution:** €2 171 791  
  - **Duration:** 48 months  
  - **Type:** Marie Curie Actions-Early-Stage Training  
  - **Starting date:** 1 March 2006
EXPECTED RESULTS

Using the *Pseudomonas aeruginosa* as a model pathogen, ANTIBIOTARGET will:

- identify key genes contributing to attachment, biofilm formation, intrinsic resistance, virulence and damage to the host;
- engineer biosensor systems for the screening of novel agents that will inhibit the infection process;
- identify natural products, enzymes and small compounds inhibiting attachment, virulence, biofilm development and promoting antibiotic susceptibility;
- develop large-scale production of pharmaceutical products identified in this project for industrial use.

Potential applications:

ANTIBIOTARGET will help the scientific community to better understand the molecular mechanisms used by *P. aeruginosa* to cause disease, and the results will be directly applicable to other bacteria of relevance to public health. The project will also generate a number of new biosensor systems in *Pseudomonas* which will be exploited for the screening of novel inhibitors of virulence factor production, as well as develop ‘designer’ organisms to increase the production of proteins and chemical compounds that can be used therapeutically to treat *Pseudomonas* infections.

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BACKGROUND
The BACELL HEALTH project was designed to gain new knowledge in the field of bacterial cell biology for the development of new products and processes. The project aimed to address both the harmful and beneficial characteristics of bacterial behaviour by undertaking an integrated and in-depth study of the response of Gram-positive bacteria to stress.

The consortium created four experimental Work Packages (WPs), each with specific milestones and deliverables: WP1 focused on a detailed understanding of how *B. subtilis* regulates its metabolism in response to environmental stresses; WP2 aimed to unravel the regulatory and biochemical processes that pathogens related to *B. subtilis* need to ‘top up’ these responses; WP3 aimed at improving the ability of commercial strains of *B. subtilis* and its close relatives to produce biopharmaceuticals; and WP4 focused on comparative genomics and network modelling.

Problem:
The major challenge for the BACELL HEALTH consortium was to understand how individual regulatory pathways are networked to maintain cellular homeostasis, using state-of-the-art post-genomic technologies; this is known as the *Cell Stress Management System*.

AIMS
The primary objective was to develop a detailed understanding of the integrative Cell Stress Management System and associated stress resistance processes that are essential for sustaining bacteria as effective pathogens or producers of pharmaceutically active proteins and peptides.

EXPECTED AND OBTAINED RESULTS
The project will develop an understanding of the regulatory networks underlying the response of environmental bacteria and pathogens to stresses encountered during infection and commercial bioprocesses.

Potential applications:
Potential new targets for antimicrobial drugs, improved production of bioactive proteins and peptides, improved commercial production strains.
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BACKGROUND
The emergence and spread of antimicrobial resistance (AMR) has become a major public health threat, and infections caused by antimicrobial resistant pathogens continue to increase in the EU and abroad. These infections cause suffering, incapacity and death, and impose an enormous financial burden on both healthcare systems and on society in general. The aim of the BURDEN project is to provide realistic estimates of the burden of disease and the costs to societies attributable to infections caused by antimicrobial resistant pathogens in member states and accession countries of the European Union.

Problem:
There is a lack of data on the treatment outcomes in infections due to antibiotic resistant pathogens, in terms of attributable mortality, prolongation of hospital care and, above all, on the economic consequences for individuals and healthcare systems and societies.

AIMS
The main specific objectives of BURDEN are:

- to generate country-specific cost models for quantifying the economic loss due to AMR;
- to determine the excess mortality, morbidity, length of stay and costs attributable to AMR;
- to present the financial impact of AMR on care in European hospitals.

EXPECTED RESULTS
The results the BURDEN partners expect include:

- identification, on a country-by-country basis, of information needs of different stakeholders for their own assessment of the burden of infectious diseases caused by antimicrobial susceptible and resistant bacterial pathogens;
- identification of incentives and counterincentives that impinge on efforts to control the spread of AMR;
- demonstration of the human and societal dimensions of infections caused by resistant pathogens and the repercussions for the healthcare systems.

Potential application:
Politicians, policymakers and public health experts will be provided with valid data in order to prioritise and plan future health political goals, as against other specific causes of morbidity and mortality in Europe.

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BACKGROUND
The CanTrain network trained both early and experienced researchers in the methodologies necessary for drug development, including target identification and development of cell-based screening assays.

CanTrain addressed infectious diseases caused by fungal pathogens, and attempted to establish approaches leading to novel anti-fungal compounds by combining the expertise of 11 partners in cellular sensor systems and signalling pathways controlling morphogenesis and virulence, model systems for host-pathogen interaction, assay development and drug screening technologies.

AIMS
The main objective of this network is to train both early and experienced researchers in the methodologies of drug development starting from target identification, target validation, development of screening assays and drug screening up to the identification of lead compounds. CanTrain aimed to develop new screens and cell-based assays for identifying novel antifungal substances. The training gained was transferable to all fields involving drug screening.

The major research objectives can be outlined as follows:

- **Objective 1** - To identify and characterize *C. albicans* and *C. dubliniensis* membrane transporters and sensors as well as downstream components which are important for the expression of virulent traits. To perform comparative genomics of *C. albicans* and *C. dubliniensis* to identify genes absent in the less virulent *C. dubliniensis*.

- **Objective 2** - To study the virulence of wild type and respective isogenic mutant *C. albicans* and *C. dubliniensis* strains using human reconstituted tissue systems and mouse macrophages as model systems.

- **Objective 3** - To study the molecular basis of host-pathogen interaction and virulence using transcriptional profiling, proteomics and biochemical approaches.

- **Objective 4** - To develop new cell-based assays for identifying potential novel antifungal substances in the context of host-pathogen interaction, including assay validation with clinical *C. albicans* and *C. dubliniensis* isolates and known antifungal drugs and screening using combinatorial compound libraries.

EXPECTED AND OBTAINED RESULTS
The partners bridged the gap between environmental stimuli inducing infection mechanism and the signal transduction pathways triggered by these stimuli. They also characterised a G protein-coupled receptor that is important for the yeast-to-hyphae transition on solid medium, and identified several potential new targets for antifungal drug discovery in both *C. albicans* and *C. dubliniensis*.

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**Project number:** MRTN-CT-2004-512481  **EC contribution:** €2 689 991  **Duration:** 48 months  **Type:** Marie-Curie Research Training Network  **Starting date:** 1 March 2005
A number of training courses were organised, including an in vitro biofilm course and a bioinformatics and microarray analysis course.

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CHANGING BEHAVIOUR OF HEALTHCARE PROFESSIONALS AND THE GENERAL PUBLIC TOWARDS A MORE PRUDENT USE OF ANTI-MICROBIAL AGENTS

BACKGROUND
CHAMP aims to promote the appropriate use of antibiotics by developing effective tools to change the behaviour of healthcare professionals, patients in primary care, and the general public on the prescription and use of antibiotics.

Problem:
Antibiotics are priority drugs and bacterial resistance is a major public health issue, and antibiotic consumption is a key driver of resistance, although the relationships are complex.

AIMS
CHAMP aims to promote, through a series of seven Work Packages, the appropriate use of antibiotics by developing effective tools to effect behavioural changes of healthcare professionals, patients in primary care, and the general public on the prescription and use of antibiotics.

EXPECTED AND OBTAINED RESULTS
CHAMP will produce an inventory of attitudes and expectations of both healthcare professionals and patients in primary care on antibiotic treatment in respiratory and urinary tract infections. It will also provide a state-of-the-art overview of behavioural interventions and public campaigns on antibiotic use and determinants of success and failure. Experts will formulate evidence-based advice to the Commission on the preferred policy in order to improve antibiotic use in European primary care.

Potential applications:
The CHAMP final report can be used to formulate future European policy in this field and to serve as a basis for national and regional strategies.

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COMBATING RESISTANCE TO ANTIBIOTICS BY BROADENING THE KNOWLEDGE ON MOLECULAR MECHANISMS BEHIND RESISTANCE TO INHIBITORS OF CELL WALL SYNTHESIS.

BACKGROUND
COBRA targeted the elucidation of the molecular mechanisms of resistance to inhibitors of cell wall synthesis in bacteria responsible for severe nosocomial and community-acquired infections. Our STREP was focused on β-lactams, the major class of antibiotics in current clinical use, and on resistance due to modifications of the cell wall synthesizing machinery and to production of β-lactamases, the most prevalent mechanisms in Gram-positive and Gram-negative bacteria, respectively.

Problem:
Antibiotics are not like other drugs in that they act against bacteria and not the human host. Therefore the evolution of resistance under the selective pressure of antibiotics after exposure of populations (human, animal) raises major therapeutical issues. This program addresses the general problem of resistance to antibiotics and concerns the understanding of the mechanisms of resistance, in particular to inhibitors of cell wall synthesis. Among these are the β-lactams, one of the most important classes of antibiotics, if not the most broadly used antibiotics worldwide. The rates of β-lactam resistance for many common species found in infections have reached high levels in the community, as well as in the hospital. While In Gram-positive organisms this resistance is mainly due to altered targets, in Gram-negative organisms, acquired resistance to β-lactams is essentially due to the presence of plasmid-encoded β-lactamases or the over-expression of chromosome-encoded β-lactamases. This latter resistance can be enhanced by associated impermeability or efflux mechanisms. Since many pathogens are multiresistant, there will be an eventual limitation in the choice of antibiotics useful for primary treatment and therefore a promotion of a vicious cycle facilitating the emergence of new resistances.

AIMS
COBRA focused on the understanding of molecular mechanisms of resistance to β-lactams and other cell wall inhibitors in clinical Gram-positive and Gram-negative pathogens.

EXPECTED AND OBTAINED RESULTS
The results anticipated by the COBRA partners included:

- understanding the role of amino acid residues in PBPs that are essential for the expression of resistance and their contribution to the structure of the PBP D, D-transpeptidase domains;
- understanding the genetic environment of the β-lactamase genes and its contribution to expression of resistance and gene dissemination.

Potential applications:
The transmission and acquisition of resistance by new strains is one of the major factors in resistance dissemination. Understanding of the transmission mechanisms is a crucial step in preventing resistance and guiding optimal antibiotic usage.

Project number: LSHM-CT-2003-5003335  EC contribution: €2 980 000
Duration: 36 months  Type: Specific Targeted Research Project
Starting date: 1 February 2004
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COMBINATORIAL BIOSYNTHESIS OF INDUSTRIAL GLYCOPEPTIDES: TECHNOLOGY, OPTIMIZATION AND PRODUCTION

BACKGROUND
COMBIG-TOP focused on the generation of new and more effective glycopeptide antibiotics by using combinatorial biosynthesis, and the faster development of new candidates by combining post-genomics techniques with modern molecular biotechnology. High-quality academic research tightly interconnected with industrial research and production processes by two participating small and medium-sized enterprises (SMEs) was vital.

Problem:
Due to the increasing frequency of nosocomial infections caused by multi-resistant bacterial pathogens, there is an urgent need for novel and better antibiotics that can supplement the existing armamentarium against pathogens.

AIMS
COMBIG-TOP aimed to generate more effective glycopeptides by combinatorial biosynthesis and to accelerate the development of promising glycopeptides through an improved fermentation process.

OBTAINED RESULTS
COMBIG-TOP generated novel peptide backbones and elucidated the glycopeptide synthesis focusing on the synthesis of balhimycin by Amycolatopsis balhimycina. Genes involved in glycopeptide tailoring reactions, such as glycosyl transfer, were collected from different glycopeptide producers or identified by genetic screening. Novel glycopeptides with altered backbones, novel glycosylation patterns and other structural modifications were developed. These drug candidates will be tested for their effectiveness as antibiotics. Flux analyses and two-dimensional (2D) maps were used to discover primary metabolism proteins up-regulated during glycopeptide production. Combined with a study of other limiting steps such as precursor uptake, bottlenecks in the glycopeptide production could be identified and eliminated, allowing the construction of an improved production strain, also usable for the novel glycopeptides generated by the project.

Potential applications:
New antibiotics for human health.
Project Coordinator

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DEVELOPMENT OF NEW GYRASE INHIBITORS BY COMBINATORIAL BIOSYNTHESIS

BACKGROUND
The bacterial enzyme DNA gyrase is well validated as a target for a number of antibacterial compounds. CombiGyrase researched and developed new drugs that are urgently needed. It represented an ideal platform to expand the diversity of potent gyrase inhibitors found in nature by methods of combinatorial biosynthesis. Combinatorial biosynthesis is a novel technology that uses genetic manipulation to improve the chemical properties and pharmacological activity of naturally occurring compounds. Using microorganisms which produce natural gyrase-inhibiting antibiotics, the CombiGyrase consortium successfully demonstrated that novel ‘designer’ antibiotics can be developed by combinatorial genetic methods. New gyrase-directed drugs, such as aminocoumarin and simocyclinone antibiotics, developed by these methods, may help to overcome problems due to clinical resistance, and may significantly expand the clinical role of the gyrase inhibitors as antibacterial agents.

Problem:
A constant threat to the population of the European Community is the ever-increasing problem of antibiotic resistance. Widespread use of antibiotics has led to the emergence of antibiotic-resistant strains. The increase and spread of resistance are a matter of serious public health concern worldwide. For example, vancomycin has long been considered as the solution to methicillin-resistant Staphylococcus aureus (MRSA) infections, but vancomycin-resistant strains of S. aureus have already begun to emerge. Nowadays, the risk of infection increases with a prolonged hospital stay, and so does failure of antibiotic therapy because of multidrug resistance.

AIMS
CombiGyrase aimed to develop new anti-infectives targeting gyrase and/or bacterial topoisomerase IV, evaluate the activity of these compounds as inhibitors of gyrase and of topoisomerase IV and of the resulting antibacterial activity against bacterial pathogens, and evaluate the suitability of these compounds as drug candidates.

The focus was on the development of derivatives of the following antibiotics, which are produced by different Streptomyces strains and represent highly potent inhibitors of gyrase:

- the aminocoumarin antibiotics novobiocin, clorobiocin and coumermycin A1;
- the mixed aminocoumarin/angucycline antibiotic simocyclinone D8;
- the mixed peptide/polyketide antibiotics cyclothialidine and GR122222X.

OBTAINED RESULTS
By using microorganisms that produce natural gyrase-inhibiting antibiotics, the CombiGyrase consortium successfully demonstrated that novel ‘designer’ antibiotics can be developed by combinatorial genetic methods.
CombiGyrase generated 33 new amino-coumarins using genetically optimised microorganisms. The structures of these compounds were elucidated, and the new antibiotics were tested for gyrase inhibition in vitro and in a cell-based reporter gene expression assay, and for their activity against bacterial pathogens. A high-throughput assay for the ATPase activity of gyrase B was established and validated with known inhibitors. A secondary assay for detecting the mode of action of novel anti-microbial compounds was validated for gyrase B inhibitors.

The consortium discovered the mode of action of a completely novel class of DNA gyrase inhibitors (simocyclinones). Simocyclinones share some structural similarities with aminocoumarins but also a number of differences. The partners found that these compounds target gyrase, and that simocyclinone D8 is a more potent inhibitor than novobiocin.

**Potential applications:**
The CombiGyrase results benefit public health by providing a road to new antibiotics, which will help to combat infectious diseases.

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BACKGROUND
Combating bacteria with antibiotics is an endless race because bacteria acquire antibiotic resistance (AR) genes easily from unknown environmental sources. An appropriate long-term public health objective would be to elucidate the molecular mechanisms behind the observed AR spread. The CRAB project explored a mechanistic approach to combat AR.

Problem:
Although mutations are responsible for some specific cases of AR, the driving force behind the problem of multiresistance to antimicrobials is gene acquisition by human pathogens.

AIMS
The principal aim of CRAB was to explore the mechanisms and process dynamics at work in each of the dissemination modules of the chain of AR genes dissemination — integrons, transposons, conjugative plasmids and stability modules — in a concerted approach.

EXPECTED AND OBTAINED RESULTS
The results CRAB anticipates and has achieved include:

- determination of the model driving integron cassette evolution;
- description of the different ways by which the three major classes of insertion sequence (IS) acquire, stabilise and vehicle AR genes;
- quantitative evaluation of the impact of IS elements on horizontal transfer within and between chosen bacterial genera, showing that IS together with conjugative plasmid constitute a powerful combination for horizontal gene transfer;
- identification of novel stabilisation modules (toxin/antitoxin) and of their functional characterisation (partly achieved);
- development of new molecular biological tools (expected).

Potential applications:
The application of state-of-the-art functional genomics will facilitate the translation of genomic data into novel products. Several of the novel approaches such as in situ monitoring of bacterial conjugation will likely lead to further developments with commercial potential.

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**BACKGROUND**

Mobile DNA elements provide a major contribution to the spread of antimicrobial resistance allowing for recruiting new resistance genes in bacterial pathogens and facilitating their horizontal spread. While much is known about individual resistance genes and mechanisms, very little is known about their molecular epidemiology. The DRESP project aimed at investigating these aspects.

**Problem:**
Antibiotic resistance remains a major clinical and public health problem, and mobile DNA elements provide a major contribution to the spread of antibiotic resistance.

**AIMS**

DRESP2 focused on the characterisation of the molecular mechanism(s) underlying mobility of genetic elements carrying antimicrobial resistance genes.

**EXPECTED AND OBTAINED RESULTS**

An exceptional amount of data (e.g. genomics, nomenclature) was produced and made available to the scientific community.

Key contributions in this extensive list of data include the description and application of new techniques for molecular replicon typing of plasmids encoding resistance to newer beta-lactams, and the description of antibiotics as signalling agents.

**Potential applications:**
- *in vitro* diagnostic medical device;
- epidemiology of drug resistances;
- prediction of drug resistance emergence to novel compounds.

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DEVELOPMENT AND DISSEMINATION OF A SCHOOL ANTIBIOTIC AND HYGIENE EDUCATION PACK AND WEBSITE ACROSS EUROPE

http://www.e-bug.eu

BACKGROUND

e-Bug is a school educational resource pack and website incorporating areas of hygiene and prudent antibiotic use to be developed and disseminated across Europe. The teaching pack with worksheets linking in with each country’s national curriculum will be accompanied by websites hosting games and interactive quizzes. Results will be used to further modify and improve the pack and website to better meet the local needs.

The consortium consists of 10 associated countries (304 million) covering 42% of the European population with the highest antibiotic use and those with large populations, thus obtaining education amongst a high percentage of high antibiotic user countries. In total, this initiative will reach 47% of the European population.

Problem:

In many European countries, antibiotic prescription rates are highest in children. Within schools, respiratory and gastrointestinal infections are a major cause of childhood illness with poor respiratory and hand hygiene contributing to increased spread of infection.

AIMS

The aims of the e-Bug project include:

- development of a school pack template incorporating hygiene and prudent antibiotic use for use across European states;
- development of a school education website for 9-11 and 13-16 years to improve health across the EU.
- dissemination of packs and marketing to collaborating partner countries.

EXPECTED AND OBTAINED RESULTS

The expected results include:

- a report on background information covering:
  - how education about hygiene, normal flora and prudent antibiotic use are covered in the schools of the associated partner countries;
  - Website resources for adults and school aged children
  - Public or school education campaigns in these areas and across Europe and if/how these have been evaluated
  - implementation strategies that have been used in the countries for educational resources.

- evaluation reports covering:
  - the ease of use and impact of the pack on children’s knowledge will be assessed in three associated partner countries through questionnaires and focus groups;
  - report on ease of accessibility and impact of the website.
Potential applications:
The e-Bug pack and website will reinforce an awareness of the benefits of antibiotics and will teach about prudent use and how inappropriate use can have an adverse effect on an individual’s good bugs and antibiotics resistance in the community.

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BACKGROUND

Clostridium difficile-associated disease (CDAD) has become the most frequent nosocomial infection in many European hospitals. Central to the control of epidemics are the deployment of assays able to rapidly diagnose and monitor the presence and spread of the organism. No such tests currently exist for these new hypervirulent C. difficile strains. The EACCAD project sought to develop the urgently required rapid, diagnostic assays in close collaboration with three small and medium-sized enterprises (SMEs).

Problem:

C. difficile is resistant to various antibiotics; it capitalises on the ensuing disruption of the normal intestinal flora to colonisation and causes disease. The effects of CDAD are devastating, both in terms of morbidity/mortality and the high costs of disease management.

AIMS

The main aim of EACCAD was the recognition of suitable targets and development of a commercial rapid test that would distinguish variant hypervirulent and antibiotic resistant strains from ordinary C. difficile strains.

EXPECTED AND OBTAINED RESULTS

1. Recognition of targets for new diagnostic tests by characterisation of hypervirulent and drug-resistant C. difficile strains. The targets are based on toxins, toxin coding regions, or other unique genes of C. difficile.
2. Availability of molecular tests and rapid membrane immunoassays for detection of the target in patient material and in bacterial isolates.
3. Validation of new developed tests for clinical diagnostics and strain characterisation.

Potential applications:

European guidelines will be formulated to diagnose CDAD and to combat outbreaks. The introduction of these tests and European guidelines increase the awareness of CDAD as an important nosocomial infection and will be of help to prevent the development of large outbreaks by new hypervirulent variants.

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Project number: LSHM-CT-2006-037870 ■ EC contribution: €1 771 000 ■ Duration: 36 months ■ Type: Specific Targeted Research Project ■ Starting date: 1 December 2006
**BACKGROUND**
A major factor affecting the emergence and survival of resistant strains is the biological cost of resistance. The EAR consortium aimed to identify antibiotic targets and antibiotics for which the resistance mechanisms have the most negative effects on bacterial fitness. The partners experimentally examined and defined in several medically important species how fitness, virulence and transmission are affected by different types of antibiotic resistance.

**Problem:**
Antibiotic resistance represents a major public health concern and economic problem.

**AIMS**
The aims of the EAR project include:
- experimentally determining how different types of antibiotic resistances affect fitness (growth and survival within and outside hosts) of several pathogenic bacterial species;
- determining if the fitness costs of resistance can be reduced by mutation and/or environmental conditions;
- developing animal experimental models to study the impact of resistance on transmission rates;

**EXPECTED AND OBTAINED RESULTS**
Firstly, the results will provide the experimental knowledge required to model and perform risk assessment for the development and spread of resistance to any given antibiotic. Secondly, the achievements accomplished here will form the knowledge base required to formulate and interpret intervention strategies that seek to reduce the rate of resistance development and achieve a reversal of the rising tide of resistance in society. Thirdly, the methodology and approaches will make it possible to identify particular attributes in high-risk resistant bacteria.

**Potential applications:**
The deliverables of EAR will aid in the development of guidelines for the clinical use and regulation of antibiotics, which may help free resources for other important health issues of EU citizens.

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BACKGROUND
The European Antimicrobial Resistance Surveillance System (EARSS), is an international network of national surveillance systems that collects comparable and validated antimicrobial susceptibility data for public health purposes. The project performs ongoing surveillance of antimicrobial susceptibility in *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Enterococcus faecalis/faecium* causing invasive infections, and monitors variations of antimicrobial resistance (AMR) in time and from place to place.

Problem:
AMR is an emerging public health problem with local, national, and international dimensions as described in ‘the Copenhagen Recommendations’. Antimicrobial resistance is clearly an emerging problem. However, the precise impact of this problem is less clear to the European and scientific community. Before being able to quantify the impact on public health it is necessary to have more comparable surveillance data available. One of the recommendations made at the EU Conference ‘The Microbial Threat’ in 1998 was that a European surveillance system of antimicrobial resistance should be set up, therefore EARSS has been established.

AIMS
EARSS aimed to obtain comparable and reliable AMR data of main indicator pathogens in Europe so as to monitor AMR in time and from place to place. It also aimed to assess risk factors for AMR and to enable policymakers and healthcare workers to monitor the impact of their interventions.

OBTAINED RESULTS
For pathogens (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Enterococcus faecalis/faecium*) causing invasive infections, resistance levels are available for important groups of antimicrobials from 27 European countries. In the EARSS annual report 2001, results are described in detail for all four pathogens collected in 2001. Aggregated information is directly available to healthcare workers, policymakers, and a wider public, at www.earss.rivm.nl.

Potential applications:
Policies to combat resistance should be specifically tailored to country and hospital level. The results, as presented in the EARSS annual report 2001, emphasise the need to implement the Council Recommendations on the Prudent Use of Antibiotics in Human Medicine. As laid down in the Council Recommendations, it has recently been decided that multidisciplinary organisations, called Intersectorial Coordinating Mechanisms (ICMs), will be established at the national level. The ICMs will be responsible for information exchange and cooperation between the parties involved at the national level.

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<th>Country (Code)</th>
<th>National Representatives</th>
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<tbody>
<tr>
<td>Austria (AT)</td>
<td>H. Mittermayer, W. Koller</td>
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<td>Belgium (BE)</td>
<td>H. Goossens, E. Hendrickx</td>
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<td>S. Kalenic, A. Tambic, A. Andrasevic</td>
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<td>D. Bagatzouni</td>
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<td>P. Urbaskova</td>
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<tr>
<td>Denmark (DK)</td>
<td>D. Monnet, R. Skov</td>
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<td>P. Naaber</td>
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<td>Finland (FI)</td>
<td>O. Lyytikäinen, A. Nissinen</td>
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<td>France (FR)</td>
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<td>Ireland (IE)</td>
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<td>K. Kristinsson</td>
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<td>Israel (IL)</td>
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<td>A. Pantusti, P. D’Ancona</td>
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BACKGROUND
ERAPharm aimed to improve existing knowledge and methods for evaluating potential risks posed by human and veterinary pharmaceuticals to the environment. The consortium addressed the different aspects of environmental risk assessment (ERA) of pharmaceuticals, including exposure modelling.

Problem:
The widespread detection of pharmaceuticals in surface waters, soils and groundwater worldwide has raised major concerns about the potential impact of these bioactive substances on the environment.

AIMS
ERAPharm aimed to advance existing knowledge and procedures for the environmental risk assessment of human and veterinary pharmaceuticals.

OBTAINED RESULTS
- Analytical methods were developed and adapted to determine selected pharmaceuticals in environmental matrices.
- Three new scenarios were identified as being insufficiently covered in the existing framework for the ERA of veterinary pharmaceuticals, despite being relevant for veterinary pharmaceuticals.
- The effects of a set of human and veterinary pharmaceuticals were studied: (1) in in vitro and low complexity bioassays, and (2) on aquatic and terrestrial organisms, at single species, population and community level using laboratory, micro- and meso-cosm and field studies.

Potential applications:
ERAPharm is expected to contribute to the establishment of more targeted and more standardised environmental risk assessment procedures for pharmaceuticals.

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EUROPEAN SURVEILLANCE OF ANTIMICROBIAL CONSUMPTION

BACKGROUND
In 2001, the European Commission funded the ESAC project which aimed to collect comparable and reliable data on antibiotic use in Europe in ambulatory and hospital care from publicly available sources, and assess the time trends in human exposure to antibiotics. In the second phase of the project (2004/07), the ESAC partners consolidated the data. In 2006, 34 countries including the 27 EU Member States, 2 Candidate Countries and 5 other nations participated in ESAC.

ESAC data have been used to explain the variation of antibiotic resistance and to assess the impact of intervention campaigns to reduce antibiotic prescribing.

Problem:
Antibiotic resistance is a major European and global public health problem, and international efforts are needed to counteract the emergence of resistance. There is a wealth of information on the prevalence of resistance in human pathogens, and these data show that there are substantial geographic differences in the proportion of resistance to various classes of antibiotics in Europe.

AIMS
The overall aim of ESAC was to consolidate the continuous collection of comprehensive antimicrobial consumption data, from ambulatory and hospital care, from the 27 Member States, 3 EEA/EFTA and 3 candidate countries (Croatia, Former Yugoslav Republic of Macedonia and Turkey).

EXPECTED AND OBTAINED RESULTS
The results anticipated by ESAC include:
- regional maps of antimicrobial use in Europe;
- hospital and individual patient consumption data linked with DRG (Disease Related Groups);
- expansion of health indicators of antimicrobial use;
- assessment of the effects of socioeconomic determinants on antimicrobial consumption of European countries.

Potential applications:
More and more countries have implemented or will implement actions to control antimicrobial resistance through the rational use of antibiotics. Their impact will be monitored based on Defined Daily Doses per 1000 inhabitants per day (DID) and other indicators of antibiotic use. The different sub-projects on ambulatory care, hospital care, nursing homes and socioeconomics will substantially deepen our interpretation of variation in antibiotic resistance.

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**BACKGROUND**
Sexually transmitted infections (STIs) in Europe are a major public health threat. Their increasing incidence; adverse impact on individual and public health; substantial economic costs; and emerging antimicrobial resistance have increased the need for pan-European approaches to their control. The ESSTI (European Surveillance of Sexually Transmitted Infections) Network aims to develop and coordinate epidemiological and laboratory surveillance of STIs in the European region in order to better inform STI prevention, care and control.

**Problem:**
The increasing incidence of gonococcal infections is of concern due to the acquisition of resistance to antimicrobials by the causative bacterium Neisseria gonorrhoeae. Antimicrobial resistance has implications for the treatment of gonorrhoea and therefore surveillance has a key role in informing about national treatment guidelines.

**AIMS**
Specific objectives include:
- operation and development of the ESSTI network with EU Member States, EFTA/EEA, Turkey;
- extension of ESSTI_ALERT, the European early warning system for unexpected and adverse STI transmission events;
- implementation of a European Gonococcal Antimicrobial Susceptibility Surveillance Project (Euro_GASP);
- delivery of training programmes on STI surveillance, lab diagnostics and STI clinical management to network participants;
- use of ESSTI website for information dissemination.

**EXPECTED RESULTS**
1. Estimates of resistance to antimicrobial agents used for the therapy of gonorrhoea across Europe.
2. Comparability of methods for determining susceptibility to antimicrobial agents for Neisseria gonorrhoeae.
3. Establishment of a panel of control strains for use in laboratories across Europe.

**Potential applications:**
Collaboration between the laboratories in this network should establish a European Gonococcal Surveillance Programme (Euro_GASP) that will monitor resistance to therapeutic agents across Europe and inform individual patient management and the production of therapeutic guidelines.

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ENABLING TECHNIQUES FOR THE DEVELOPMENT OF A NOVEL CLASS OF PROTEIN ANTIBIOTICS

BACKGROUND
Antibiotics’ resistance to pathogens is a major threat to public health and safety, increasing the risk of mortality, especially in hospital settings. This issue also includes preparedness to deal with bio-terrorism. Currently, the antibiotics market is dominated by small molecule classes, which all face increased drug resistance and require product differentiation. While this remains a primary focus in antibiotics development, new concepts for entirely new classes of substances for the treatment of bacteria, fungi, viruses and protozoa are urgently needed.

AIMS
ET-PA aimed to develop an open, generic platform to enable the development of a new class of protein-antibiotics. The key technology (REPPs) is based on a principle that is proprietary to one of the participating small and medium-sized enterprises (SMEs), and consists of rationally modified, single-chain class II restriction enzymes (REs) fused to cell penetration peptide (PP) sequences that selectively allow microbial cell penetration. The consortium sought to fuse an appropriate cell PP sequence to an engineered RE that includes both subunits in a single chain, so as to produce a ‘REPP’ construct capable of microbial cell penetration and autonomous folding to an active unit within the cell.

EXPECTED AND OBTAINED RESULTS
The major milestone was to provide a clear proof of concept for the introduction of the class of REPP molecules as antibiotics. Lead substances for further preclinical development were expected. The ET-PA consortium has defined that for a successful targeting of prokaryotic pathogens by REPP antibiotics, these molecules must clearly accomplish four tasks cross the outer cell wall barriers of bacteria and bind to the membrane surface;

1. enter into the cytoplasm by translocating or otherwise crossing the cytoplasmic membrane;
2. fold the enzymatic portion to the active form, a process whose rate limiting step in natural REs is mainly defined by the rate of the dimerisation;
3. specifically bind to and cut DNA damaging the bacterial genome.

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Invasive Bacterial Infections
Surveillance in European Union

BACKGROUND
Standardisation of epidemiological and laboratory methodologies across the EU allows valid overviews and comparisons to be drawn on the epidemiology of invasive Haemophilus influenzae (H. influenzae) and Neisseria meningitidis (N. meningitidis) diseases. These two diseases are both rare, and the EU-IBIS project allowed the pooling of data to increase the power of an epidemiological analysis.

Problem:
The bacteria N. meningitidis and H. influenzae are an important cause of invasive disease, including meningitis, septicaemia and epiglottitis, across Europe. These bacterial infections contribute to morbidity and mortality, particularly in young children, and represent an important public health problem.

AIMS
The objectives of the project included:

- improving the epidemiological information on invasive meningococcal and Haemophilus influenzae disease within the EU;
- improving the laboratory capacity to accurately characterise the isolates of H. influenzae and N. meningitidis;
- evaluating the impact of vaccination with conjugate vaccines on the epidemiology of H. influenzae and N. meningitidis;
- comparing the impact of vaccination with conjugate vaccines produced by different manufacturers and according to different schedules;
- focusing on a wider collaboration with non-EU countries and Candidate Countries.

EXPECTED AND OBTAINED RESULTS
The EU-IBIS network contributed to strengthening disease-specific surveillance in the EU. Through the use of standard EU case definitions and an agreed minimum dataset, the comparability of surveillance data allows valid comparisons to be drawn across the EU. Improved laboratory capacity for diagnosis and characterisation of circulating organisms will also contribute to making valid comparisons between countries possible, and will enable accurate reporting on emerging strains, or rapid reporting. A number of countries with unreconciled datasets will be encouraged to work towards full reconciliation of their clinical and laboratory data. This will improve the data contributed to EU-IBIS, but will also have beneficial value to the individual countries.

Improvements in surveillance data have already occurred within EU-IBIS participant countries, and will continue to be seen, especially in Accession Countries. The standardised epidemiological and microbiological data gathered by EU-IBIS give the ability to detect whether changes in disease epidemiology are driven by environmental factors or vaccine impact.

Equally, the network enables a concerted response to such changes with appropriate surveillance strategies or public health

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interventions. This was demonstrated by the establishment of two short-term N. meningitidis rapid reporting systems over the lifetime of the project; a sentinel W135 reporting system following the Hajj 2000 outbreak, and a B:2a/B:2b rapid reporting system to identify instances of capsule switching following the introduction of meningococcal C vaccine.

Attainment of standardised, quality surveillance data for H. influenzae and N. meningitidis throughout the EU provides a platform for other studies of meningococcal disease and H. influenzae. This has already been seen in the EU-MenNet-EU-IBIS collaboration.

Potential applications:
This project will allow the more rational development of vaccine policy in Europe and ensure that this policy is evidence-based. Rapid dissemination of changes in the epidemiology of an infection which may have public health significance is possible through the established EU-IBIS network. The standards set by EU-IBIS for epidemiological surveillance and for methods used in reference laboratories provide models of good practice from which EU Member States, Candidate Countries and non-EU countries can learn. Early dissemination of advances in therapy and in public health control measures can be facilitated through this network, which can lead to harmonisation of guidance on meningococcal disease.

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EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

BACKGROUND
EUCAST was initiated by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the national breakpoint committees in Europe to give Europe uniform breakpoints for antimicrobial susceptibility testing. EUCAST harmonised breakpoints for all existing antimicrobials at the end of 2008. Moreover, through the cooperation between EUCAST and EMEA, several new antimicrobials have received European breakpoints through the EUCAST breakpoint process.

Problem:
There is a lack of uniform antimicrobial breakpoints in Europe, both for therapy and for antimicrobial resistance surveillance, as well as a lack of a uniform European processes for setting breakpoints for new antimicrobial agents.

AIMS
The main objective was to provide Europe with harmonised antimicrobial breakpoints for existing drugs and a pathway through which new drugs can receive uniform breakpoints in Europe. The EUCAST consortium also sought to cooperate with all expert groups and European agencies with an interest in antimicrobial breakpoints, and to set up a website for the dissemination of key materials.

OBTAINED RESULTS
1. Standard operating procedures (SOP) regulating the cooperation between EUCAST and EMEA is operative.
2. Breakpoints for several new drugs have been determined.
3. Breakpoints for existing drugs have been harmonised for aminoglycosides, glycopeptides, fluoroquinolones, linezolid, carbapenem, aztreonam, cephalosporines, macrolides, penicillins and miscellaneous drugs.
4. All cooperation (EFSA, EMEA, EARSS etc) is operative.
5. Subcommittees on antifungal drugs, interpretative rules in susceptibility testing and anaerobe bacteria are operative.
6. A European disk test for routine susceptibility testing is being developed.

Potential applications:
Europe is in need of uniform breakpoints for the categorisation of bacteria and fungi in susceptible, intermediate and resistant categories for therapy with antimicrobial drugs and for the measurement of antimicrobial resistance development.
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INHIBITION OF NEW TARGETS FOR FIGHTING ANTIBIOTIC RESISTANCE

BACKGROUND
Peptidoglycan (PG) biosynthesis and bacterial cell morphogenesis are related phenomena and are totally specific to bacterial cells without even remotely equivalent systems in eukaryotic cells. The enzymes and proteins involved in these processes are thus promising targets for the design of new antibiotics. Interfering with the activities of the participating enzymes or with the protein-protein interactions that take place along these metabolic pathways should perturb the bacterial cell cycle and, hopefully, supply new weapons to fight dangerous pathogenic organisms such as the methicillin-resistant *Staphylococcus aureus* (MRSA).

Problem:
The increase in antibiotic resistance is a global problem, both for nosocomial and community-acquired infections.

AIMS
The aim of the EUR-INTAFAR network is to find new targets for antibiotics and to use the knowledge amassed on the antibiotic-resistant forms of the ‘old’ targets for the design of more efficient molecules.

OBTAINED RESULTS
1. Transpeptidases (Tpases) or Penicillin-Binding-Proteins (PBPs) are the targets of β-lactam antibiotics. However, some pathogenic bacteria such as *Streptococcus pneumoniae* and the methicillin-resistant *Staphylococcus aureus* MRSA have acquired transpeptidases that are resistant to most clinically useful β-lactams. Various novel methods have been devised to test inhibitors prepared by the chemist partners. The partners have shown that lactivicin, the only known natural compound exhibiting such properties, is active against clinically isolated penicillin-resistant *S. pneumoniae* strains. Crystallographic studies performed with *S. pneumoniae* PBP 1b reveal that the inactivation reaction involves opening of both cycloserine and lactone rings of lactivicin. Thus, lactivicin derivatives will be useful in the search for antibiotics active against β-lactam resistant bacteria.

2. Screening for inhibitors of glycosyltransferase (GTase) activity yielded 30 potential inhibitors among which two were found to inhibit GTase activity of E.coli PBP 1b.

3. The steps preceding transglycosylation and transpeptidation result in an outward-oriented lipid II. They involve the synthesis of lipid II by MraY and MurG followed by translocation of the disaccharide-peptide moiety across the cytoplasmic membrane. The synthesis and translocation have been studied.

4. Only two clinically useful antibiotics are presently available which target the intracellular steps leading to the soluble PG precursors and one of them (cycloserine) might be withdrawn in the near future. All the intermediate metabolites have been prepared and a
novel class of MurD inhibitors has been identified. The structure of an enzyme inhibitor complex has been solved.

5. In *S. pneumoniae*, new enzymes participating in teichoic acid biosynthesis have been identified and the long-standing problem about why *S. pneumoniae* requires choline for growth was solved.

6. An innovative high-throughput system has been developed for screening chemical compound libraries in microspots (EU patent application submitted, February 2008).

Potential applications:
This project is of prime importance as a springboard to re-activate the important therapeutic area of antibiotic drugs. A better understanding of the physiology and biochemistry of bacterial cell morphogenesis and peptidoglycan biosynthesis will create new avenues for the design and synthesis of efficient antimicrobials. This will make new opportunities available for companies of different sizes to develop these compounds until they reach the clinical level.

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INTEGRATED POST-GENOMIC APPROACHES FOR THE UNDERSTANDING, DETECTION AND PREVENTION OF ANTIFUNGAL DRUG RESISTANCE IN FUNGAL PATHOGENS

http://www.chuv.ch/imul/euresfun

BACKGROUND
The EURESFUN (EUropean RESistance FUNgal) network used genomics-based integrated approaches to study antifungal resistance in relevant fungal pathogens (Candida, Aspergillus). Using microarray strategies and systematic deletion/over-expression approaches, the network sought to unravel potential novel targets for antifungal drug discovery, but also to yield diagnostic tools and mutations suitable for use in resistance monitoring and surveillance.

Problem:
The frequency of fungal infections has been steadily increasing in the human population worldwide over the past decades. Several fungal pathogens cause severe fungal infections in hospitals. Among them, the most important are Candida albicans, C. glabrata and Aspergillus fumigatus. C. albicans accounts for more than 50% of all fungal infections, causing both superficial and disseminated infections, while C. glabrata infections account for 10 - 20% of the cases.

The exposure of fungal pathogens to antifungal agents has different outcomes, one of which is the development of resistance.

AIMS
The aims of EURESFUN included:

- designing new therapeutic strategies to improve the efficacy of existing antifungal therapy;
- establishing and using cell-based arrays for drug target genes for drug discovery by a small and medium-sized enterprise (SME);
- establishing data on resistance incidence and prevalence, and linking clinical data on susceptibility to known antifungals with a therapy outcome.

EXPECTED AND OBTAINED RESULTS
EURESFUN anticipated the following results:

- identification of specific mutations linked to antifungal resistance;
- identification of cellular components and isolation of their inhibitors;
- collection of strains displaying a wide range of susceptibility to known antifungals and associated with molecular epidemiology data;
- generation of novel diagnostic tools enabling genotyping, species identification and antifungal resistance monitoring.

Potential applications:
The diagnostic tools would rapidly detect mechanisms of resistance, impact on the costs associated with the treatment of fungal infections and reduce the social burden of these infections. The European industry’s competitiveness in the field of diagnostics would be reinforced.
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INTEGRATION OF VIRAL GENOMICS WITH CLINICAL DATA TO PREDICT RESPONSE TO ANTI-HIV TREATMENT

BACKGROUND
The EuResist project has developed a European integrated system for clinical management of antiretroviral drug resistance. The system will provide the clinicians with an online prediction of response to antiretroviral treatment in HIV patients, thus helping the clinicians choose the best drug combinations for any given HIV genetic variant.

Problem:
While combination antiretroviral therapy has made HIV infection a treatable condition, eradication of infection is not yet achievable and antiretroviral therapy needs to be administered as a prolonged, possibly lifelong treatment. Long-term toxicity, difficulty in adhering to complex regimens, possible pharmacokinetics problems, and intrinsically limited potency are all factors favouring the selection of drug-resistant viral strains. Development of drug resistance is nowadays a major cause for treatment failure.

AIMS
The EuResist objectives included:

- integration of biomedical information from three large and expanding European databases;
- combination and availability of the best performing models into the final EuResist Combined Predictive System.

EXPECTED RESULTS
The EuResist Integrated Database has been realised by physically merging the founding ARCA, Arevir and Karolinska databases.

A Standard Datum has been defined in compliance with the definition proposed by the Forum for Collaborative HIV Research (www.hivforum.org).

Different predictive methods have been developed and compared. Three engines have been chosen as the best performers: Generative-Discriminative (GD), Evolutionary (EV) and Higher order interaction, or Mixed Effects (ME).

The EuResist Web interface has been developed under the guidance of virologists and physicians.

Potential applications:
The project can be considered as a pilot for Hepatitis C virus (HCV) and Hepatitis B virus (HBV) since a large antiviral treatment intervention has been started and the chronic nature of both of these viruses is expected to lead to the development of drug resistance.
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BACKGROUND
Eurofungbase targeted the creation of conditions and facilities within Europe to widely apply all genomics technologies in filamentous fungal research. This is expected to expand knowledge and benefit Europe’s biotechnology industries, as well as help improve the prevention and treatment of fungal disease.

The project focused on several filamentous fungi for different reasons; one was Aspergillus nidulans for its long record of use as a fungal model organism.

The human pathogen Aspergillus fumigatus serves not only as a model pathogen, but becomes more and more a serious threat to human health. The project contributes to create the conditions and facilities within Europe to widely apply all genomics technologies in filamentous fungal research. This will greatly expand our knowledge about filamentous fungi. This new genomics information will thus be beneficial to Europe’s biotechnology industries and help to improve the prevention and treatment of fungal disease.

Problem:
Widespread genomic research leads to enormous amounts of data stored in many small databases across Europe. For integrated European genomic research, it is important that such data become easily accessible for all researchers.

AIMS
The aim was to develop a strategy to build up and maintain an integrated, sustainable European genomic database required for innovative genomics research of filamentous fungal model organisms of interest. This database will become a crystallisation point for related systems and could then be integrated and conserved in a central European genomic database.

EXPECTED RESULTS
Eurofungbase anticipated several results:

- contribution of the community to the manual annotation of important fungal genomes through annotation jamborees;
- realisation of an integrated sustainable fungal genomic database;
- realisation of a fungal genomics knowledge base for the Eurofungbase community and the European fungal biotech industry;
- intensified collaboration between the members of the network;
- individualised training of a next generation of young scientists in fungal genomics and biotechnological research.

Potential applications:
Fungi play an important role in White Biotechnology (e.g. biomass saccharification, biorefinery). The results of this project will find their way in new experimental approaches in those areas.
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For the full list of participants and a list of members of the Fungal Industrial Platform, see http://eurofung.net/index.php?option=com_content&task=blogcategory&id=13&Itemid=14 and http://eurofung.net/index.php?option=com_content&task=blogcategory&id=12&Itemid=15 online.

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BACKGROUND
The study of infectious disease, which is established in Europe in the form of various national research centres and a considerable number of laboratories, needs a multidisciplinary approach that brings together the different disciplines of molecular biology, immunology, cell biology and structural biology. The Network of Excellence is forging permanent links and structures between the different disciplines.

Problem:
There is an urgent need for research in the field of infectious diseases. Many pathogens become increasingly resistant to available drugs and antibiotics. The prevalence of antibiotic resistances is increasing in both developed and developing countries. They impose an important socioeconomic burden on the public, industry and the healthcare system.

AIMS
EPG seeks to stimulate multidisciplinary collaborative research activities, create a European training facility for teaching of scientists and physicians, and foster biotechnological applications and technology transfer to European companies.

EXPECTED RESULTS
The expected deliverables are innovations in the areas of diagnostics, drug and vaccine development. The project will promote discoveries leading to the development of innovative diagnostic tools, the identification of new antigens and the deciphering of host defence mechanisms. The consortium will analyse the mechanisms conferring to the development and spread of antibiotic resistances among bacteria.

EPG will establish a higher standard in the infectious diseases teaching field. Thus, a permanent and durable structure will be created that will maximise the contributions of European scientists to this area.

Potential applications:
EPG will promote discoveries leading to the development of innovative diagnostic tools, the discovery of novel anti-infectious agents and their targets, the identification of new antigens and the deciphering of host defence mechanisms.

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EUROPEAN COHORT COORDINATING NETWORK ON HIV DRUG RESISTANCE

BACKGROUND
EuropeHIVResistance will create and maintain a pan-European cohort with a network of virological reference centres in over 30 European countries.

Problem:
HIV resistance to one or more antiretroviral drugs is spreading throughout the world. Of major concern is the possibility that no effective antiretroviral drugs will be available for newly infected patients.

AIMS
The aim of EuropeHIVResistance is to create a large pan-European cohort for studying the appearance, spread, virological determinants and clinical consequences of HIV resistance under joint standards linked to a common shared self-sustainable database.

EXPECTED RESULTS
The EuropeHIVResistance network will make a major contribution in the following ways: by (i) expanding HIV-drug resistance surveillance and follow-up activities to a pan-European level; (ii) decreasing the fragmentation of HIV resistance research in central and eastern Europe; (iii) increasing the level of virological expertise and skills in HIV resistance in this region; and (iv) securing the desired exchange of good practices between the HIV/AIDS cohorts in Europe and the World Health Organization (WHO).

Potential applications:
This network will help develop better guidelines for the treatment and prevention of HIV, as well as for the prevention of drug-resistant HIV variants transmission.

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SURVEILLANCE OF TUBERCULOSIS IN EUROPE

BACKGROUND
EuroTB was established in 1996 to improve the contribution of epidemiological surveillance to tuberculosis (TB) control in Europe. The project coordinated the surveillance of TB in the 53 countries of the World Health Organization’s (WHO) European Region through contact points based in the national TB surveillance institutions that report standardised data annually to EuroTB.

Problem:
TB is a directly communicable condition and transmission most often occurs following the inhalation of droplets from a person with active TB. It is a serious disease which can lead to death, disability and chronicity.

AIMS
The mission statement of EuroTB: ‘To improve the contribution of surveillance to TB control in Europe’.

The general objectives of the project included:
- coordinating and enhancing surveillance of TB in Europe;
- monitoring and comparing trends in TB morbidity in Europe and characterising vulnerable populations;
- contributing to the harmonisation of the investigation of TB contacts and the management of TB outbreaks at the national and EU levels.

EXPECTED AND OBTAINED RESULTS
The results of EuroTB activities are documented in the following manner:

1. yearly reports: ‘Surveillance of tuberculosis in Europe’;
2. European TB data sets: case-based (1) and aggregated (6);
3. MDR-TB: reports and a genotype website;
4. final report on molecular surveillance of MDR-TB (end-2007);
5. scientific papers and communications;
6. ad hoc reports on expert consultations following country visits to enhance surveillance;
7. quarterly EuroTB newsletter.

Potential applications:
1. Formulation of policy relating to TB and MDR-TB.
2. Scientific pursuit.
3. Use for preparation of reports, lectures, and presentations by experts.
4. Information for awareness campaigning.

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THE Fungal cell wall AS A TARGET FOR ANTIFUNGAL THERAPIES

BACKGROUND
Fungal pathogens represent the major eukaryotic agents of serious infection in European countries. Infections due to *Candida albicans* and *Aspergillus fumigatus* are the most common and clinically important pathogens and were therefore the focus of this project. There is an urgent need to generate new, efficacious, non-toxic compounds with broad-spectrum antifungal activity. The challenge for FUNGWALL was to investigate mechanisms of fungal cell wall synthesis in order to identify new antifungal targets to control human fungal infections in Europe.

AIMS
The cell wall of pathogenic fungi is a good target for the development of new drugs for the following reasons: (1) The fungal cell wall is required for fungal cell integrity and is essential for fungal growth and for virulence; (2) Polysaccharidic components of the cell wall are unique to fungi and consequently, putative inhibitors of the biosynthetic pathways responsible for cell wall construction can be potent antifungals.

The objectives of FUNGWALL centred on the assembly of the cell wall polysaccharide skeleton. The project partners focused on the identification of new-generation antifungals that target fungal cell wall biosynthesis.

OBTAINED RESULTS
The achievements of the project have placed Europe in a world-leading position for analysis of fungal cell wall. The coupling of biochemical and genetic methodologies was extremely synergistic for tackling this problem and has given a unique flavour to FUNGWALL.

The 36-month FUNGWALL project led to many achievements, including:

- validation of chitin synthesis as a legitimate target for antifungal chemotherapy;
- elucidation of the mode of action of aminocandin through various genomic strategies;
- development of methodologies to analyse carbohydrate-protein interactions;

Thus, several new drug targets were identified during the course of FUNGWALL:

- chitinases and endo β1,3 glucanases;
- new transglycosidases remodelling β glucans;
- O-mannosyltransferases.

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BACKGROUND
GenOSenpt used a multidisciplinary fundamental genomics approach (gene expression, structural genomics and population genetics) to examine genetic predisposition to sepsis. The partners aimed to standardise protocols for genotyping, facilitate application of new knowledge in functional and structural genomics, harmonise high-throughput genotyping and quality control between major European centres, and contribute to reducing sepsis-related mortality in European healthcare.

AIMS
The major milestones of GenOSenpt were:

- consensus definitions and the setting up of an inclusion and exclusion criteria database;
- collection of blood samples from about 2,500 patients all over Europe;
- blood genotyping and genetic testing;
- identification of relevant candidate genes and their genomic variations;
- genetic epidemiology study to be performed in European intensive care units (ICUs);
- definition of a diagnostic Single-Nucleotide Polymorphism (SNP) set.

EXPECTED AND OBTAINED RESULTS
The expected results of GenOSenpt are that, among others, it will:

- contribute to unravelling the genetic predisposition of sepsis;
- define novel candidate genes by gene expression studies;
- include genes directing pathways of the host immune response to infection and inflammation, and of programmed cell death.

Potential applications:
The GenOSenpt findings will contribute to reducing sepsis mortality and morbidity in European ICUs.

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GRACE is a Network of Excellence focusing on the complex and controversial field of community-acquired lower respiratory tract infections (CA-LRTIs). The promiscuous use of antibiotics to treat LRTIs accounts for a majority of the community burden of antibiotic use and contributes dramatically to the rising prevalence of resistance among major human pathogens. GRACE will combat antimicrobial resistance through integrating centres of research excellence and exploit genomics in the investigation of CA-LRTIs.

**Problem:**
CA-LRTIs are the leading reason for seeking medical care. Yet there are few conditions in medicine that are so controversial. These uncertainties have resulted in prescriptive promiscuity, which largely explains the escalating antibiotic resistance of common bacterial respiratory pathogens in the community. There are no good studies of sufficient size on detecting bacterial aetiology of LRTIs and on diagnosis of Community-acquired pneumonia (CAP) in primary care.

**AIMS**
GRACE aims to strengthen European human and microbial genomic research excellence, focusing on CA-LRTIs, which is the leading reason for seeking medical care and consuming antibiotics. The hallmark of the Network of Excellence created by GRACE will be the integration of research platforms creating a European-wide infrastructure to investigate and improve the management of CA-LRTIs.

**EXPECTED AND OBTAINED RESULTS**
- Delivery of an Internet Web portal under a common corporate identity integrating all IT functions.
- Development of a platform, GOS (GRACE Online System), serving internal purposes and dissemination of results to the public.
- Establishment of a microbial diagnostic network of laboratories to develop novel rapid genome-based diagnostic tests for the detection of pathogens.
- Identification of susceptibility genes by using candidate genes as well as a genome-wide association approach in more severe LRTIs, such as invasive pneumococcal disease cases. As a result of candidate gene studies, the list of known susceptibility genes has been extended to eight in total (i.e. MBL, CD32, CRP, PTPN22, TLR1-6-10, MAL/TIRAP, NFKBIA, and NFKBIE).
- Detection and analyses of new viruses to contribute to our understanding of the mechanisms of LRTIs, and development of methods that may be applicable for analysis of the etiology of other infectious diseases.
- Establishment and evaluation of the molecular methods that will be used using an existing collection of pneumococcal isolates.
- Variability in both prescription and antibiotic choice across Europe.
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HEALTH ALLIANCE FOR PRUDENT PRESCRIBING, YIELD AND USE OF ANTIMICROBIAL DRUGS IN THE TREATMENT OF RESPIRATORY TRACT INFECTIONS

http://www.happyaudit.org/

BACKGROUND
The HAPPY AUDIT project aims to strengthen the surveillance of respiratory tract infections (RTIs) in primary healthcare in Europe through the development of intervention programmes targeting general practitioners (GPs), parents of young children and healthy adults. The intervention programme will curb the occurrence of bacterial resistance by reducing the prescription of unnecessary antibiotics for RTIs and by improving the use of appropriate antibiotics in suspected bacterial infections.

Problem:
Infections caused by resistant bacteria lead to increased mortality, prolonged hospital stays and increased costs.

AIMS
HAPPY AUDIT aims to change people’s habits towards the prudent use of antimicrobial agents (antibiotics) via the Audit Project Odense (APO) method, developed and successfully tested by GPs in the Nordic countries.

EXPECTED RESULTS
The HAPPY AUDIT results will be available at local and European level, and in the education sector, ensuring that the message has a deep impact on the younger generation. The intervention will have strong visual potential that will make it appealing to people at all levels. The ambition is to create a differentiated teaching material that is suited for different age groups.

Potential applications:
The project will show examples on best practice and how GPs will benefit from intervention activities. They will underline the message that there are barriers to overcome, but that the changing of behaviour towards prudent use of antibiotics will lead to a healthier society. In this way the intervention will create goodwill, understanding and backing for the public.

The HAPPY AUDIT is using a bottom-up approach in the trial to change behaviour among professionals. Patients may act as professionals if their knowledge about their diseases is relevant and rational. Especially for young people, familiar with the modern electronic communication messages, there will be a tendency to discuss with doctors and nurses about new therapies as well as question old ones.

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BACKGROUND
Considerable efforts have been made to date to harmonise data on nosocomial infections (NI) and antibiotic resistance (AR) in Europe. As a result, large variability in preventive practices and outcomes across countries has become evident. Based on this experience, the IPSE project aimed at resolving these persisting differences through the following approaches:

- providing health services with timely information, evidence-based guidelines and educational tools to manage effectively the risk of NI and AR;
- strengthening the status of professionals involved in infection control activities;
- fostering the control of the emergence and spread of multiple resistant organisms in the intensive care unit (ICU) through an integrated surveillance programme;
- monitoring the level of achievement of the NI and AR control programmes.

Problem:
Considerable efforts have been made to date to harmonise data on healthcare-associated infections (HAI) and antimicrobial resistance (AMR) in Europe. As a result, large variability in preventive practices and outcomes across countries has become evident.

AIMS
IPSE aimed to reduce significant differences that persist in the risks associated with HAI and AR in the healthcare of countries in Europe.

EXPECTED AND OBTAINED RESULTS
IPSE results include the following:

- harmonisation and support for professional profiles and training for infection control practitioners;
- European standards and indicators for public health surveillance and guidelines for the control of HAI and AMR;
- event warning and rapid exchange on NI and AMR;
- sustaining and extending HELICS NI surveillance in Europe;
- improving surveillance and control of antibiotic resistance and hygienic precautions in the ICU;
- understanding the interaction of antibiotic consumption, infections and resistance patterns in the ICU;
- feasibility of surveillance of HAI in European nursing homes and home care.

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CONTROL STRATEGIES FOR VISCERAL LEISHMANIASIS (VL) AND MUCOCUTANEOUS LEISHMANIASIS (MCL) IN SOUTH AMERICA: APPLICATIONS OF MOLECULAR EPIDEMIOLOGY

BACKGROUND
The LeishEpiNetSA project involves comparative investigations between endemic areas for visceral leishmaniasis (VL) and mucocutaneous leishmaniasis (MCL) in Paraguay, Peru, Brazil and Venezuela, and will strengthen local capacities for research and Latin American-European collaborations.

LeishEpiNetSA will develop a full range of microsatellite markers and multi-locus sequencing typing (MLST) of housekeeping genes for the Leishmania braziliensis complex and for L. guyanensis. It will also establish in South America the procedures for microsatellite and MLST analysis for L. infantum, which have been developed and proven as epidemiological tools by a European network.

Problem:
A full and detailed understanding of the transmission cycles and molecular epidemiology of VL and MCL is necessary to develop disease control and surveillance.

AIMS
The overall aim is to apply molecular methods to improve the understanding of the epidemiology of the subgenus Vannia and L. infantum in South America.

EXPECTED RESULTS
A range of new epidemiological tools will be produced. Distribution of drug-resistant genotypes will be mapped. A wealth of data will be deposited in a new database, linked to a European database. An expanded South American repository for Leishmania will be established and cooperation will be improved between South American researchers. A series of publications and reports will be written to disseminate findings from the project.

Potential applications:
Improved strategies for surveillance and control, with consequent benefits to public health and the alleviation of poverty.

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FULLY AUTOMATED AND INTEGRATED MICROFLUIDIC PLATFORM FOR REAL-TIME MOLECULAR DIAGNOSIS OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

BACKGROUND
Methicillin-resistant *Staphylococcus aureus* (MRSA), a virulent organism resistant to many drugs, is responsible for many nosocomial and community-acquired infections. Effective diagnostics is a strategic key element in the campaign against the spread of MRSA, allowing better infection surveillance and control measures, as well as more efficient patient treatment and/or isolation options. MagRSA will develop a new diagnostics platform providing a fast, simple and accurate identification of MRSA from clinical samples.

Problem:
According to the World Health Organization (WHO), resistance of *Staphylococcus aureus* to methicillin, its usual antibiotic, increased from 2% in 1975 up to 60% today in some areas and no new antibiotic is expected on the market for many years.

AIMS
MagRSA seeks to develop a new diagnostics platform that will provide a fast, simple, automated and accurate identification of MRSA from clinical samples. The simplicity of the proposed technology concept — integrating cost-effective and widely available components — allows for the provision of low cost systems, a prerequisite condition for the large adoption of molecular tests by hospitals.

EXPECTED RESULTS
**Procedure improvement:** The steps of the diagnostic protocol were significantly improved in terms of specificity, sensitivity and turn-around time (three hours instead of six hours) and relies on the following steps:

1. The diagnostic protocol relies on a new and clinically validated procedure that consists of a direct one-step enrichment of *S. aureus* present in either nasal or inguinal swabs, followed by DNA extraction of immunocaptured bacteria and their identification by multiplex sequence amplification using real-time quantitative PCR.

Potential applications:
MagRSA’s diagnostics platform will have potential applications in molecular diagnostics and be the most growing segment within the global in vitro diagnostics market.

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BACKGROUND
Malaria is one of the three major infectious diseases. Although the disease is prevalent in the tropics and subtropics, it has caused a global emergency. Between 300 to 400 million cases with 1 million to 2 million deaths are recorded each year. A rapidly increasing resistance to antimalarial drugs calls for focused novel strategies to combat the disease. MalariaPorin is an interdisciplinary project aimed at taking genomic information forward to drug development. The Plasmodium falciparum genome project aimed at the accelerated discovery of novel antimalarial drug targets. Using P. falciparum genome data, MalariaPorin identified a single water/glycerol channel (aquaglyceroporin of Plasmodium falciparum (PfAQP)) present at the parasite/host interface. It is the only member of the aquaporin family encoded in the P. falciparum genome.

AIMS
The goals of MalariaPorin were to assess the suitability of PfAQP as an anti-malarial drug target and generate the conditions for further development of such drugs.

OBTAINED RESULTS
Significant progress was made in various areas related to the project, involving fields as diverse as Plasmodium physiology, pharmaceutical chemistry and biophysics. MalariaPorin provided first insights into osmotic protection systems of apicomplexan intracellular parasites, obtained fundamental and novel data on glycerol metabolism of P. falciparum, redefined known and specified new aquaporin protein structures that determine pore selectivity, identified therapeutically targetable aquaporin structures, and established solid and usable assay systems for testing potential aquaporin blockers, among others.

Potential applications:
PfAQP has the potential to be used as a target for malaria treatment. It is further envisioned that MalariaPorin may become the starting point for a wider strategy to assess the role of aquaporins in pathogenic parasites, such as Toxoplasma gondii, Trypanosoma brucei and Trypanosoma cruzi, and their potential use as drug targets.

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DEVELOPMENT OF NOVEL MANAGEMENT STRATEGIES FOR INVASIVE ASPERGILLOSIS

http://www.manasp.org

BACKGROUND
The overall objective of the MANASP project was to develop new treatment strategies for Invasive Aspergillosis (IA) — the major infectious complication of treating haematological malignancies with intensive chemotherapy or haematopoietic stem cell transplantation (HSCT).

AIMS
The aims of MANASP included:

- development of immunotherapeutic strategies for IA;
- development of improved diagnostic tests for IA with commercial potential;
- validation of a dendritic cell (DC)-based vaccine immunotherapy strategy in animal models to generate protective immunity against Aspergillus;
- use of genomic and proteomic techniques to identify new Aspergillus targets that interact with the host’s immune system.

EXPECTED AND OBTAINED RESULTS
The results of the MANASP include:

- identification of different pattern recognition receptors in response to A. fumigatus and their role in activating DCs;
- identification of PAMPs of A. fumigatus useful for immunotherapy strategies;
- characterisation of Aspergillus-specific T-cell response in healthy individuals;
- development of an assay to detect Aspergillus DNA with high specificity;
- commercialisation of the assay into an affordable and rapid diagnostic test.

Potential applications:
Incorporation of diagnostic tests will facilitate research trials of new antifungal agents or other novel therapies, and wider application of this technology will enable the treatment of other groups of patients (outside the Haematological Malignancy field).

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BACKGROUND

Recent genomic technologies allow the study of global physiological processes in microbes. Their application to the study of pathogens enables researchers to search for new medicines to combat infection, avoid the emergence of resistance against them, and help anticipate therapies for new emerging diseases and devise treatments. Predictive microbiology may also be used to anticipate the presence of unexpected potential pathogens. Both industrial and sustained public sector efforts are needed to fully develop the promising potential of this research frontier of the microbial world.

Problem:

The ability to effectively treat microbial infections will reduce morbidity, and have a positive impact on health management policies. The discovery of new antibacterial agents against resistant micro-organisms is an urgent and vital need. The social costs incurred by the incidence of infectious diseases in the population at large, and in particular the elderly and the productive age sectors, are enormous. Hospitalisation costs per patient run above about 500 € per day. Curbing the spread of resistant pathogens will result in the attainment of high standards in human health care, it will reduce social and public healthcare costs and will therefore have a beneficial impact on the citizens.

AIMS

The micro-MATRIX workshop aimed to discuss microbial functional genomics as a powerful and innovative tool; to discover new cellular targets that would be used to counteract bacterial resistance to antibiotics; and to further avoid the generation and spread of new resistances.

OBTAINED RESULTS

The workshop conclusions were summarised in a report (http://www.cnb.csic.es/~mvicente/micro-MATRIX+cover.pdf) submitted to the Commission. It provided a roadmap to implement a research activity based on functional genomics to tackle the problem of antibiotic resistance and discovery. A summary of the report was presented at the PathoGenoMics ERA-NET Constituent Assembly in Berlin on 14 October 2004.

Potential applications:

Genomics can contribute to combating antibiotic resistance and comparative genomics yields information on the universality of targets in important pathogens. Functional genomics helps us understand how to avoid the path to resistance, and genomics research will contribute to increasing the amount of antibiotic generated by the producer organisms.

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Infections caused by antimicrobial-resistant bacteria (AMRB) account for an increasing proportion of healthcare-associated infections in European hospitals, particularly in intensive care units (ICUs). Increased prevalence of resistance to antibiotics in major hospital pathogens is associated with adverse outcomes of patients affected, and includes delayed appropriate therapy or even failure of therapy, as well as increased mortality.

While the optimal strategies for control of AMRB remain debated, understanding the dynamics of resistance and the relative contribution of the most important determinants of dissemination of AMRB (cross-transmission via contacts and antimicrobial selective pressure), is needed to better define these strategies. The integration in these approaches of rapid molecular diagnostic testing for AMRB carriage may improve the timeliness and efficacy of control measures.

The overall objective of MOSAR is to provide advanced knowledge in the dynamics of transmission of AMRB, and address the controversies surrounding control measures by testing different strategies to combat the emergence and spread of antimicrobial resistance, focusing on endemic or emerging AMRB in hospitals, now spreading into the community.

The results anticipated by the MOSAR partners include the following:

1. development of standards for conventional methods for detection of AMRB in screening samples;
2. development and validation in the clinical setting of high-throughput molecular-based methods for detection of resistant bacteria in screening for...
carriage of AMRB in clinical samples, and assessment of their cost-utility;

3. assessment from prospective, multi-centre studies in areas with high prevalence of antimicrobial resistance, of the relative efficacy and cost-effectiveness of different control strategies including enhanced standard precautions;

4. development of mathematical models integrating the contribution of the intrinsic epidemicity of MRSA, of cross-transmission and of antibiotic use in the dynamics of resistance, to be translated into user-friendly interfaces for use by infection control personnel.

Potential applications:
Results from MOSAR will inform healthcare workers and decision-makers on strategies for forecasting and mastering antimicrobial resistance. The project’s results should increase awareness of nosocomial pathogens such as vancomycin-resistant enterococci (VRE) as an emerging cause of hospital acquired infections.

MOSAR will contribute to developing the next generation state-of-the-art technologies of diagnostic tests. Existing molecular tests and the newly developed technologies will be adapted to the different needs of the laboratories and countries participating in MOSAR.

Knowledge gained through MOSAR will help format education and training of healthcare personnel and beyond.

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IDENTIFYING NOVEL CLASSES OF HIV INHIBITORS

BACKGROUND
The objective of the NewHiv Targets project was to design novel screening assays allowing the identification of novel classes of HIV inhibitors.

Problem:
Despite the success of highly active antiretrovirals to control HIV replication in infected patients, at least in countries that can afford these treatments, new drugs are still needed. Widely used drugs mainly target two viral enzymes: reverse transcriptase and protease. However, about 20% of patients cannot tolerate antiviral cocktails in the short term, and long-term treatments are often associated with severe side effects. There is also increasing concern about the spread of drug-resistant HIV variants.

AIMS
The project partners aimed to identify lead compounds that could impact HIV through new mechanisms. Academic experts in virology and cellular biology joined forces with antiviral-research specialists and pharmacologists to perform anti-HIV high-throughput screening (HTS) assays. The partners defined one unexploited viral target, for which there are no available inhibitors: the critical step of viral release from the cell. This novel target was chosen because important recent discoveries have shed new light into the molecular mechanisms of virus budding, thereby rendering this critical step in the HIV lifecycle a feasible target for drug development.

EXPECTED AND OBTAINED RESULTS
The NewHiv Targets partners designed one cell-based assay that did not require the use of infectious virus, allowing for the screening of chemicals libraries. As proof of concept, they screened 2 000 compounds, and were able to identify one interesting hit. In secondary analysis with infectious HIV, this compound displayed very little antiviral activity.

The next aim was to extend the screening to a higher number of compounds (2 libraries of 20 000 and 4 000 compounds. The partners sought to further document the activity of the first hit. More fundamentally, they are studying the mechanisms of HIV-1 assembly and transfer through cell-to-cell contact.

Potential applications:

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BACKGROUND
Tuberculosis (TB) is one of the most deadly infectious diseases in the world. The high rates of patient non-compliance lead not only to more than 3 million deaths per year, but also to the creation of chronic, infectious, drug-resistant TB strains, against which almost all existing antibiotics are ineffective or prohibitively toxic. The outcome of the NEWTBDRUGS project would lead to new drugs that would shorten the duration of TB treatment, improve latent TB infection treatment and be effective against multidrug-resistant TB (MDR-TB).

Problem:
The key problem in TB treatment is the six- to eight-month-long treatment duration, which often leads to non-compliance. Patients frequently get better quickly on an intense course of antibiotic chemotherapy and therefore stop taking the drugs before the infection is eliminated. MDR-TB has become a major health problem, not only in developing countries but also in neighbouring countries of the European Community. In the face of the HIV/AIDS epidemic, new ‘sterilising’ drugs with shorter regimens are needed that can significantly increase patient compliance, substantially reduce the rate of emergence of antibiotic resistance, materially decrease the costs of treatment and prevent progression from latent infection to active disease. New strategies are urgently needed for combating the problems of TB treatment.

AIMS
The NEWTBDRUGS consortium aimed to apply their integrated strategy of drug development by structural analysis of novel targets, virtual and real screening-based identification of leads, new organic synthetic chemistry and functional evaluation of best hits in in vivo animal models.

EXPECTED AND OBTAINED RESULTS
This study made a number of scientific breakthroughs including:

- solution of the 3D structure of several persistence-related drug targets of M. tuberculosis;
- development of new assays for screening drugs that kill persistent M. tuberculosis.

Potential applications:
At least one of the leads identified and developed in this project will enter clinical trials in humans for treating persistent TB, in cooperation with pharmaceutical companies active in manufacturing the existing TB drugs.

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Project number: LSHP-CT-2005-018729 ■ EC contribution: €1 800 000 ■ Duration: 36 months ■ Type: Specific Targeted Research Project ■ Starting date: 1 September 2005
BACKGROUND

New Medicines for Tuberculosis (NM4TB) aims to successfully develop new drugs for the treatment of tuberculosis (TB) through an integrated approach implemented by a team that combines some of Europe’s leading academic TB researchers with a major pharmaceutical company and three small to medium-sized enterprises (SMEs), all with a strong commitment to discovering new anti-infective agents. NM4TB has a comprehensive portfolio of potential and validated targets, plus several novel, proprietary anti-TB agents in its drug development pipeline. Among the validated targets are several enzymes involved in highly druggable areas such as cell wall biogenesis, nucleic acid synthesis and central metabolic pathways for which assays amenable to high-throughput screening are available. Intensive efforts will focus on rapidly emerging targets that impact upon two as yet untouched areas of the physiology of M. tuberculosis signal transduction pathways and persistence.

Problem:

TB is one of the oldest diseases known to man and has infected one third of the world’s population. As a result, someone dies from the disease every 15 seconds and 30 million more people will lose their lives to TB in the next decade. Although directly observed short-course chemotherapy is available to treat the disease, this treatment is old, slow and inefficient by the current standards of the pharmaceutical industry. Here, the project partners will employ the most innovative approaches to identify and validate targets for new drugs, and implement the screening and medicinal chemistry processes required to identify lead compounds for the generation of candidate drugs.

AIMS

NM4TB aims to successfully develop new drugs for the treatment of TB with the following desired properties:

- high potency to reduce treatment duration;
- activity against persistent bacilli;
- inhibition of new target classes;
- activity against multidrug resistant TB;
- specificity for Mycobacterium tuberculosis.

EXPECTED RESULTS

The NM4TB consortium anticipates the following results:

- development and implementation of novel enabling technologies required for drug development.
- target validation in well-established, ‘druggable’ areas such as the central metabolism, cell wall and nucleic acid synthesis;
- generation of the structural information for as many targets as possible, acting iteratively in the drug development process.
- assay development and screening of deep chemical libraries encompassing ‘Active’ to ‘Hit’, ‘Hit’ to ‘Lead’
progression; ‘lead’ optimisation activities that give rise to candidate drugs.

Potential applications:
The proposed research will result in:

- the development of new technologies and assays for TB drug development;
- the discovery of new classes of lead compounds for fighting TB;
- the lead optimisation and progression to candidate drug status.

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TAILORING OF NOVEL PEPTIDE COATINGS AND THERAPEUTICS DERIVED FROM A NEWLY IDENTIFIED COMPONENT OF THE HUMAN INNATE IMMUNITY AGAINST RESISTANT INFECTIONS

http://npari.org/

BACKGROUND
The apoE and apoB human proteins have recently been linked to the innate immune system. Peptide sequences derived from these proteins have been shown to have varied anti-infective properties that can be modified by small changes to the core peptide sequence. Thus, the apoE and apoB peptides exhibit antibacterial, antifungal and antiviral properties, and present an excellent opportunity to develop novel therapeutics and medical device coatings.

Problem:
Despite major advances made in the development of numerous classes of antimicrobial agents to treat serious life threatening infections, microorganisms are becoming increasingly resistant to the agents developed by man.

AIMS
The aims of the NPARI consortium were to fully exploit the exciting properties of this novel peptide class. Specifically, the consortium aimed to target peptide sequences into two areas: coating agents for medical devices and therapeutics agents.

EXPECTED AND OBTAINED RESULTS
1. The design of a small peptide library tailored to the proposed exploitable application of the project.
2. Determination of the activity spectrum of active peptides and ranking of peptide variants.
3. Optimisation and toxicity profiling of active peptides.
4. Efficacy profiles against a panel of resistant organisms growing as biofilms.
5. Pharmacological and efficacy evaluation of peptides in a range of models.

Potential applications:
The exploitation of this new class of antimicrobial peptides offers the potential to develop new therapeutics against a range of the most resistant and problematic organisms facing European infectious disease clinicians.

SME Participation
A vital component to the project is the participation of several small and medium-sized enterprises (SMEs) who have expertise in the fields of drug development. This, combined with the academic expertise of the remaining partners, allowed for an experienced and focused consortium.

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VETERINARY PHASE THERAPIES AS ALTERNATIVES TO ANTIBIOTICS IN POULTRY PRODUCTION

BACKGROUND
Phages are very specific in killing a limited range of bacterial strains, cf. antibiotics, and do not cause infections of animals or plants. Studies have shown phages to be effective in removing contamination from poultry carcasses, and in killing pathogens in the intestinal tract of live poultry and in eggs.

The Phagevet-P project focused on trials in live poultry to evaluate the importance of safety and quality factors including phage choice and production, and modeling of the infection and curing process. Alternative strategies were also considered for potential constraints related to development of phage-resistant strains of pathogens, mass application causing environmental concerns, and destruction of phages by stomach acidity following oral administration.

Problem:
Antibiotics are currently being phased out of food animal production but alternative methods are needed to combat bacterial diseases in food animals, and to control transmission of pathogens responsible for food-borne illnesses to humans.

AIMS
Phagevet-P aimed to evaluate the potential use of phages as alternatives to antibiotics in poultry production and to characterise the efficacy of phages from farm-to-fork.

The first scientific objective is to establish that in live poultry, treatment with specific phages can reduce or eliminate the occurrence of the two pathogens responsible for the majority of human food-borne illness, namely Salmonella and Campylobacter spp.

The second major objective is to establish that this protection of the live birds from infection, provides poultry products for human consumption that have greatly reduced contamination levels with these two pathogens.

OBTAINED RESULTS
The lytic spectra of the phages were determined on a group of more than 200 clinical and food isolates of different serotypes of both pathogens. The genomes of some of the Salmonella phages were examined and shown not to carry any Salmonella genes, indicating a very low likelihood of carriage and potential transfer of pathogenic traits. In vivo trials showed that the phages selected and characterised offer a good potential to control Salmonella and Campylobacter in vivo, but its efficacy is time dependent.

Potential applications:
Reduction or elimination of the widespread use of antibiotics in poultry feed and replacement by prophylactic application of phages in large-scale poultry rearing.
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BACKGROUND
The advances of the PNEUMOPEP project were new targets, identification of completely new lead compounds, a new approach to adjunctive therapy and a new method of delivery of the compounds.

*Streptococcus pneumoniae* (*S. pneumoniae*) imposes a huge disease burden on humans. There is a pandemic of multidrug resistant pneumococci and treatment is compromised. Even if antibiotics kill the bacterium, they can fail to prevent death from neurological damage after meningitis, due to the acute toxemia.

The first event in toxemia is the release of pro-inflammatory or toxic pneumococcal products, probably exacerbated by antibiotics. The pneumococcal toxin pneumolysin fulfils both definitions: it is directly toxic to mammalian cells and it stimulates the release of inflammatory mediators from host cells.

For this reason and because the toxin is essential for the survival of the bacterium in vivo, pneumolysin was a target for this project. A second target was the cell surface proteinases involved in adhesion and invasion, which are important virulence factors for the pneumococcus. These proteins represented new targets and their validation as targets was completed.

The new treatment will be based on binding peptides isolated from a series of large phage display libraries or based on small molecules identified by high throughput screening.

Problem:
*S. pneumoniae* imposes a huge disease burden on humans: it is the number one cause of pneumonia and it is the second most common cause of meningitis.

AIMS
PNEUMOPEP aimed to identify small molecules and peptides that inhibit the activity of pneumolysin on pneumococcal surface proteins, *in vitro* and *in vivo*.

OBTAINED RESULTS
The consortium obtained lead compounds for development of pneumococcal drugs.

Potential applications:
The results of the project would contribute to the treatment of pneumococcal diseases.

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BACKGROUND

PREVIS provided an integrated platform to study important and unexplored aspects of pneumococcal disease/pathogenesis, epidemiology/transmission and molecular mechanisms for resistance development and even if the program now has come to an end the network will continue to study invasive disease potential in a collected study from all the countries as well as pneumococcal meningitis in Europe. Hence the project has created novel interactions and collaborations that will continue even after the funding has ceased from the EU commission.

Problem:

Streptococcus pneumoniae remains among the most important causes of life-threatening community-acquired diseases such as pneumonia, septicemia and meningitis, particularly in high risk groups such as young children, HIV+ individuals and the aged. The annual global mortality rate is over one million. Streptococcus pneumoniae is also the major cause of upper respiratory tract infections (URTI) such as otitis media, and URTIs are one of the most common reasons for visits to doctor’s offices and for antibiotic prescriptions. As many as 60% of healthy children attending day-care centers have been found to be colonized with pneumococci in the nasopharynx, which therefore appear to be a main reservoir for this pathogen. Drug resistant clones (DRPn) emerging from this major ecological reservoir are widely spread in Europe, threatening effective antibiotic therapy. For decades, penicillin has been the drug of choice for treating pneumococcal infections, but increasing levels of penicillin resistance, up to 50% in some areas, has resulted in the use of alternative antibiotics.

Properties affecting virulence of the organism, such as adherence, invasion and transmission of the bacteria, and human host factors have to be investigated and correlated to the development of resistance and to the acquisition of resistance markers. Also, antibiotic consumption may be an important factor affecting transmission and selection for resistance determinants. A better knowledge of molecular mechanisms involved in resistance and of host-pathogen interactions affecting pneumococcal infections would lead to improved intervention, prevention and treatment strategies of these common community acquired infections.

AIMS

The objectives were to examine:

- survival and growth in the antibiotic rich milieu making it essential that bacteria acquire genetic traits of resistance;
- successful drug-resistant strains to compete with other members of the species for colonisation, geographic spread and disease in the human host.
OBTAINED RESULTS
Results of PREVIS include:

- non-typeable pneumococci (NTPn) have diverse genetic backgrounds;
- a novel bacterial factor — pilus — is important for colonisation, virulence and the inflammatory response in mice;
- TLR(toll-like receptor)9 deficient macrophages are defective in pneumococcal phagocytosis and killing.

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BACKGROUND
Malaria remains one of the most devastating diseases of the developing world, causing more than 1 million deaths and 300 million to 500 million clinical cases each year. Although four Plasmodium species infect humans (P. falciparum (P. f.), P. vivax, P. ovale and P. malariae), most deaths are caused by the severe complications of P. f. malaria. Malaria-related morbidity and mortality are increasing mainly as a consequence of drug resistance as observed with the two most widely used antimalarial drugs: chloroquine and sulfadoxine-pyrimethamine. To combat malaria, new drugs are urgently needed.

The READ-UP project targeted the identification of a new drug candidate for malaria. Starting from one series with antimalarial activity, the project would realise hit-to-lead optimisation through molecular modelling, testing of new chemical entities in vitro and in vivo and pharmacological, pharmacokinetics, toxicological and mechanisms studies.

AIMS
Following the drug discovery process until the pilot-scale production, the objective was to propose one antimalarial drug candidate with two back-ups for further pre-clinical studies.

EXPECTED AND OBTAINED RESULTS
An initial series of new stable compounds was developed. In a first synthetic series, several compounds presented anti-plasmodial properties and preliminary in vitro and in vivo studies led to the identification of one hit. Based on the excellent in vitro and in vivo results already obtained, READ-UP will develop new structural analogues using the same innovative approach. The in vitro and in vivo results obtained will be further improved by the application of optimisation techniques, through the ‘Drug Discovery’ process that the READ-UP partners will implement. Moreover, the READ-UP innovative strategy should allow designing chemically stable compounds, which may have a longer duration of action in vivo.

Potential applications:
Application of READ-UP scientific breakthroughs into approved new medicines.

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NOVEL OPPORTUNITIES TO DEVELOP VACCINES TO CONTROL ANTIBIOTIC RESISTANT BACTERIA: FROM THE TRIALS BACK TO THE LABORATORY

BACKGROUND
Antibiotic resistant bacteria are rapidly spreading worldwide, making it increasingly difficult to treat infections in large communities as well as creating a major public health problem. Vaccination is proposed as one of the best tools to stop the spread and development of antimicrobial resistant microorganisms. However, the analysis of the effects of using conjugated vaccines against Streptococcus pneumoniae, Haemophilus influenzae b and Neisseria meningitidis has shown some paradoxes and some interesting aspects that led to a re-thinking of how immunity to polysaccharide is elicited following vaccination and how memory is acquired.

The workshop proposed by REBAVAC — involving some of the most important experts in vaccination, immunology and bacterial resistance — represented a very important opportunity in Europe to discuss the implication of the results of ongoing research on the use and development of vaccines to fight antibiotic resistant bacteria.

Problem:
Staphylococci and vancomycin-resistant Enterococci are causing nosocomial infections, while other pathogens like pneumococcus, effectively treated in the past with penicillin, are now resistant to a broad spectrum of antibiotics.

AIMS
The overall aim of REBAVAC was to organise a European workshop in which worldwide leading experts in vaccine research and immunology met with healthcare providers, industry representatives and public health experts to discuss critical issues.

EXPECTED AND OBTAINED RESULTS
The workshop provided European researchers with the newest trends and directions of research in the area of vaccines to antibiotic-resistant bacteria. It was a good occasion to envisage the exploitation of new vaccination strategies.

The outcomes of the workshop are expected to compel the European research and industry to move towards more efficient/efficacious vaccines and vaccination strategies, and to find novel immunisation ways to optimise the use and formulation of currently available vaccines to fight antibiotic resistance.

Potential applications:
The impact of the scientific workshop and of the correlated activities planned by REBAVAC is expected to be very strong in the field of developing new strategies against antibacterial resistant infections.

The involvement of the European industry and research groups in the vaccine field should fuel the design of novel vaccination strategies, leading to improved control of infectious diseases and stronger well-being for everyone.

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BACKGROUND
The EU banned growth-promoting antibiotics in 2006, and livestock producers need alternative ways of obtaining similar production benefits to maintain profitability and competitiveness against overseas producers. Improving the health and safety of animal products reaching the consumer, including those resulting from organic farming, is also important.

REPLACE is examining plants, plant extracts and other natural materials as safe alternatives to feed antimicrobials. The project will link fragmented research carried out with different animal species across Europe and provide a platform for the rational production of a new generation of natural feed additives.

Problem:
The main fear was that antibiotic resistance would arise from the use of antibiotics in animals, and in turn possibly transmit this resistance to human pathogens. Anthelmintics are also becoming increasingly problematic in preventing parasitic infections, and safe alternatives are needed. Aquaculture is a growing sector within the EU and antimicrobials are common in combating the problems associated with intensification. Finding a growth promoter of natural origin will have benefits for environmental safety and awareness as well as the meeting the demand for a healthier food chain. Ways must also be found to improve the healthiness and safety of animal products reaching the consumer, including those from organic farming.

AIMS
The overall aim is to derive safe alternatives to antimicrobials, based on plant extracts and other natural materials.

EXPECTED RESULTS
The expected outcome will be a catalogue of plant extracts that can be used as potential replacements for antibiotics in the animal feed industry. The major deliverables are to find natural materials that suppress E. coli, Salmonella and C. perfringens infections, suppress parasites and their egg production in ruminants.

Potential applications:
The generated knowledge will allow the project results to achieve market penetration for the new or modified products, and provide safe alternatives to former feed additives.

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EVALUATING PHYSIOLOGICAL AND ENVIRONMENTAL CONSEQUENCES OF USING ORGANIC WASTES AFTER TECHNOLOGICAL PROCESSING IN DIETS FOR LIVESTOCK AND HUMANS

BACKGROUND
The SAFEWASTES project targeted the development of innovative biotechnology for processing and purifying organic materials from the food and plant-based extracts industries.

Problem:
The industrial processing of fruits and vegetables as well as the extraction of herbs produces millions of tonnes of organic waste, by-products and residues each year. These waste materials are costly and contribute to environmental problems.

AIMS
SAFEWASTES aimed to find innovative ways for generating novel, high added value products, and to demonstrate that there is potential in recycling their organic by-products for the purpose of producing new products acceptable to all stakeholders.

OBTAINED RESULTS
By-products of the plant processing industry were (re-)extracted before and after enzymatic fermentation and investigated phytochemically, in vitro and partly also in vivo in farm animals. A remarkable antioxidant, anti-inflammatory and anti-adhesive (antimicrobial) activity was found in vitro and in vivo.

Potential applications:
The results of SAFEWASTES will help food manufacturers use scientific approaches to meet consumer demands for safer, higher-quality food. The project will also boost European competitiveness. Improved recycling of organic wastes should reduce the load on landfills and cut methane production by composting. SAFEWASTES improved cooperation between industry and academia, generating new employment in biotechnological processing.

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NOVEL THERAPEUTIC AND PROPHYLACTIC STRATEGIES TO CONTROL MUCOSAL INFECTIONS BY SOUTH AMERICAN BACTERIAL STRAINS

BACKGROUND
Enteric and respiratory diseases remain a major cause of mortality during neonate life and childhood within developing countries. The SavinMucoPath project is focusing on bacteria that enter through or colonise enteric and respiratory mucosa, i.e. *Streptococcus pneumoniae*, *Salmonella enterica* serovar *Enteritidis*, and *Bordetella pertussis*. The selected bacterial pathogens are associated with important rates of morbidity and mortality in South America, especially in young children and those in the low socioeconomic bracket. Moreover, the strains and serotypes that cause infections are unique to the developing countries in this area and consequently, basic research and development of therapies and vaccines tailored to these local strains have been deserted by the European and North American scientific communities.

Problem:
Mucosal tissues represent the major sites of infection by pathogenic microbes and the study of mucosal pathogens is therefore relevant for combating infection and reinforcing immunity. Thus, enteric and respiratory diseases remain a leading cause of mortality worldwide. This proposal focus on mucosal bacterial pathogens that are of main importance for public health in Latin America. The strategic objective is to confront the emergency caused by specific strains of *Streptococcus pneumoniae*, *Salmonella* spp., and *Bordetella pertussis* — through the improvement of knowledge on molecular pathogenesis and the development of novel therapeutic and prophylactic interventions.

AIMS
The main objectives are to fuel understanding of the host-pathogen interaction and to develop novel mucosa-specific therapeutics and vaccines to control bacterial infections. Our strategies are based on the exploitation of innate defence mechanisms triggered by pathogen conserved molecules and pathogen-specific factors.

EXPECTED RESULTS
The consortium expects to identify molecules from the selected bacteria that activate specifically protective mucosal innate immunity so as to block infections at the port of entry of bacteria and stimulate antigen-specific responses through mucosal cells.

We will develop cell and rodent models for high throughput screening of pathogen components to ultimately bring candidate experimental immuno-interventions against enteric and respiratory infections to clinical trials within the next FP

Potential applications:
SavinMucoPath should contribute to the development of appropriate treatment of the corresponding diseases, especially during childhood. The project will have a major impact in the field of development of mucosal immuno-stimulators — adjuvants that specifically control mucosal infections.

Project number: INCO-CT-2006-032266  ■  EC contribution: €1 699 908  ■  Duration: 36 months  ■  Type: Specific Targeted Research Project  ■  Starting date: 1 October 2006
This effort may have a “transdisease” impact on anti-microbial treatments and vaccine strategies for different infectious diseases. If successful, the screened molecules may have an impact on the overall existing vaccines and antibiotherapy. A successful outcome of SavinMucoPath will substantially contribute to the further development of innovative and effective projects against any neglected mucosal infections.

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TARGETING MALARIA TRANSMISSION THROUGH INTERFERENCE WITH SIGNALLING IN PLASMODIUM FALCIPARUM GAMETOCYTOGENESIS


BACKGROUND
Inhibiting the transmission of the malaria parasite from infected humans to the mosquito vector would be of considerable interest in the context of malaria control, especially for preventing the dissemination of drug-resistant genotypes. Since only sexual forms of the parasite (the gametocytes) are infective to the mosquito, blocking gametocytogenesis would prevent transmission. But the molecular control of gametocytogenesis is not understood. Our laboratories have independently brought significant contributions to the characterisation of (i) components of signalling pathways, some of which are likely to be involved in parasite sexual differentiation, and (ii) proteins expressed at the onset of gametocytogenesis, such as Pfpg27 and Pfps16. The SIGMAL project aimed to generate an integrated picture of the early events of sexual development at the molecular level.

Problem:
Malaria is a major public health problem in most of the developing world, and the morbidity and mortality burden inflicted by this disease on many developing countries hinders socioeconomic development. The emergence and spread of malaria parasites that are resistant to existing anti-malarials also exacerbates this problem. A way to control the spread of drug-resistant parasites would be to prevent transmission of the parasite from infected humans to the mosquito vector. To infect a mosquito, the parasite must first develop into specialised sexual forms, the male and female gametocytes, while in the bloodstream of the human host. Although proteins that are specifically expressed at the onset of gametocyte formation have been characterised, the molecular mechanisms controlling this phenomenon remain to be elucidated. It is likely that intracellular signalling, and particularly the phosphorylation of proteins, is involved in gametocyte differentiation and further stages of the sexual cycle. Indeed, reverse genetics data generated within the SIGMAL consortium have already identified protein kinases (the enzymes responsible for protein phosphorylation) and other signalling molecules as essential for Plasmodium sexual development. Interference with these enzymes may provide lead compounds for the development of transmission-blocking drugs.

AIMS
SIGMAL aimed to raise understanding of gametocyte formation, in particular by characterising the signalling pathways involved, and to identify inhibitors of protein kinases that may inhibit sexual development of the parasite, and thus interfere with malaria transmission.

OBTAINED RESULTS
The SIGMAL partners obtained:

- improved knowledge of the basic biology of malaria parasites, particularly with respect to cell differentiation;
- validation by reverse genetics of novel molecular targets for transmission-blocking intervention;

Project number: LSHP-CT-2004-012174 | EC contribution: €969,000 | Duration: 27 months | Type: Specific Targeted Research Project | Starting date: 1 March 2005
identification of protein kinase in cycle of malaria parasites.

Potential applications:
SiGMAL will provide a list of validated targets for transmission-blocking drugs in the context of anti-malarial chemotherapy.

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BACKGROUND

Molecular diagnostics of microbial pathogens is an integral part of modern medicine. The growing need for direct genotyping and/or the screening of the transcriptome calls for the development of alternative technologies. The SLIC consortium planned to develop a cost-effective platform for the identification bacterial species based on the SLIC-Nanobiosystem.

Using tmRNA transcripts of the bacterial ssrA gene, the project partners were able to detect, quantify and identify bacterial species in a single homogeneous assay format. The SLIC-Nanobiosystem consists of a self-assembled lipid bilayer membrane that integrates a synthetic ligand-gated ion channel (SLIC). The SLIC comprises a capture molecule that can specifically bind a given analyte, a process that is monitored via electrical impedance spectroscopy. With this system, the effect from even a few channels can be resolved, thus providing an ultra-sensitive, highly stable and versatile biosensor platform.

The consortium planned to employ transcripts (tmRNA) of the ssrA gene to identify bacterial species present in clinical samples. These transcripts occur in high abundance and contain a core sequence that is species specific, a feature that was used to identify infectious disease pathogens.

AIMS

SLIC targeted the development of a cost-effective platform for the identification of bacterial species based on the SLIC-Nanobiosystem.

EXPECTED AND OBTAINED RESULTS

The identification of the different bacterial tmRNA transcripts would be achieved by displaying a library of nucleic acid capture probes on the SLIC. This will enable species identification and discrimination between one or more species present in the sample if mixed species infection is present.

Since the detection equipment will be based on electronics, the realisation of miniaturised/compact and cost-effective instruments will be possible.

Potential applications:
The consortium’s approach will lay the foundation for a new generation of multiparametric molecular testing systems that will open novel opportunities within the area of point-of-care applications in the clinical diagnostics market.

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FUNCTIONAL GENOMIC CHARACTERISATION OF MOLECULAR DETERMINANTS FOR STAPHYLOCOCCAL FITNESS, VIRULENCE AND DRUG RESISTANCE

BACKGROUND
The spread, survival and prevalence of antibiotic resistant clones of Staphylococcus aureus represent an important problem for human health. It is crucial to determine the key parameters required for virulence, nasal colonisation and survival in the environment in order to elucidate how these combine to produce epidemic strains. This requires a detailed knowledge of the bacterial components necessary for the above processes. The StaphDynamics project aims to define these bacterial components, which in themselves may form novel targets for prevention and control.

Problem:
Infections with antibiotic resistant microorganisms dramatically decreases the quality of life of patients and leads to a higher morbidity in specific risk groups, such as the elderly, immune-suppressed patients and children.

AIMS
The primary aim of StaphDynamics is to identify important molecular determinants for fitness, virulence and drug resistance of S. aureus that may serve as future targets for drug and vaccine development, and to fight staphylococcal infections.

EXPECTED RESULTS
The StaphDynamics results include:

1. identification of novel molecular signatures of resistant clones;
2. identification and validation of novel targets for drug and vaccine development;
3. development of informed strategies for combating resistant clones at the European level.

Potential applications:
StaphDynamics will create an important knowledge base needed to foster European competitiveness in the area of antibiotics research.

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BACKGROUND
The bacterial protein secretion process can benefit human health through the biotechnological production of biopharmaceuticals, but secreted bacterial toxins and virulence factors represent a major threat as well. The Twin-arginine translocation (Tat) machinery represents a recently discovered yet widely conserved system for bacterial protein secretion.

The Tat machine project sought to eliminate existing bottlenecks in the Tat nanomachine that limit biopharmaceutical production in Bacillus, E. coli and Streptomyces, as well as to characterise the structure and function of Tat nanomachines from selected Gram-positive and Gram-negative bacteria.

Problem:
The Tat protein transporter system differs from all other known protein translocases. The system has significant potential for biomedical and biotechnological research and exploitation.

AIMS
The aims of Tat machine included:

- exploiting the unique abilities of the system for the production of biomedically important, heterologous proteins;
- solving the three-dimensional (3D) structure of representative Tat machines.

EXPECTED AND OBTAINED RESULTS
The deliverables of Tat machine include:

- development of super-secreting strains of B. subtilis and Streptomyces coelicolor, capable of exporting heterologous proteins with high efficiency;
- understanding of the overall role of Tat in a limited series of pathogenic bacteria;
- in-depth understanding of the Tat translocation mechanism was achieved by a combined biochemical/genetic analysis of the Tat translocation process.

Potential applications:
Tat machine will provide solutions to the industry and create a knowledge base that will foster European competitiveness in the area of antibiot-}
ics and biotechnology research.

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Project number: LSHG-CT-2004-005257 EC contribution: €2 000 000 Duration: 48 months Type: Specific Targeted Research Project Starting date: 1 November 2004
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ESTABLISHING A TB TREATMENT EFFICACY MARKER

BACKGROUND
The focus of the TB Treatment Marker project was on investigating the possibility of creating a novel approach to monitor tuberculosis (TB) treatment efficacy, which would lead to a more rational use of drugs, and reduce the incidences of resistance to TB medication.

Since the war in the 1990s in Guinea Bissau, laboratory facilities for diagnosing TB have been inadequate. As part of the project, the consortium built a functional TB laboratory.

Of some 2,000 screened TB suspects, 400 diagnosed with active TB were included in the study by December 2006 and an 8-month treatment follow-up was carried out.

Problem:
No method to successfully monitor the efficacy of TB treatment currently exists. Upon diagnosis, patients are treated for TB with a course of medication lasting approximately six to nine months. If the primary treatment fails, a stringent and time-consuming analysis is made to select appropriate and effective antibiotics as a second-line treatment.

Mortality is high in both TB suspects and in TB patients during treatment, and simple and inexpensive methods for identifying individuals at risk are warranted.

AIMS
TB Treatment Marker aimed to determine whether the blood plasma protein suPAR (soluble urokinase Plasminogen Activator Receptor) is elevated in patients with active TB, and carries a prognostic value during the treatment period, as well as whether suPAR levels decrease in patients that respond to therapy.

EXPECTED RESULTS
An analysis of treatment efficacy and mortality in TB suspects and during the TB treatment programme were carried out at the end of 2007.

Potential applications:
A simple laboratory analysis that can reduce mortality and shed light on TB treatment efficacy can have a major influence on the lifetime expectancy and quality of life of people in Guinea Bissau and in all areas of the world where TB and HIV (human immunodeficiency virus) cause despair and mortality.

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DEVELOPMENT OF A MOLECULAR PLATFORM 
FOR THE SIMULTANEOUS DETECTION OF 
MYCOBACTERIUM TUBERCULOSIS RESISTANCE 
TO RIFAMPICIN AND FLUOROQUINOLONES

BACKGROUND

Treatment success and containment of drug-resistant tuberculosis (TB) rely on 
a timely laboratory diagnosis. In view of this, a versatile and user-friendly molecular 
platform was proposed for the identification of *Mycobacterium tuberculosis* in 
clinical specimens and the simultaneous detection of resistance to two key anti-TB 
agents: rifampicin and fluoroquinolones.

Problem:
The management and control of multidrug resistant tuberculosis (MDRTB) relies on sol-
?id laboratory support. The spread of MDRTB can be prevented only if patients with drug-
 resistant disease are detected and treated with a combination of effective drugs.

AIMS

TB-DRUG OLIGOCOLOR targeted the de-
velopment of a modification of the DIAPOPS 
technique (detection of the immobilised 
amplified product in one phase system) 
for the early detection of resistance to 
rifampicin in *M. tuberculosis*, as well as the 
detection of resistance to fluoroquinolones. 
It also aimed to perform a small preclinical 
evaluation in three laboratories to evalu-
ate the combined platform directly using 
clinical samples and early liquid cultures.

EXPECTED RESULTS

TB-DRUG OLIGOCOLOR antici-
pated the following results:

- development of a molecular tool 
  for the rapid detection of rifampicin 
  resistance in *M. tuberculosis* di-
  rectly from clinical samples;
- integration into a single solid support 
  of the capacity to detect resistance 
  to fluoroquinolone and confirm the 
  identification of *M. tuberculosis*.

Potential applications:
The analysis of genes involved in the resist-
ance to key anti-TB agents will enhance 
the understanding of microbial genetic 
events leading to TB treatment failure. 
Additionally, mutated gene sequences will 
become available for eventual use in drug 
target research and tool development.

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BACKGROUND

TRAINAU is a multidisciplinary Early Stage Training site on identification, characterisation and assessment of public health risks associated with non-human use of antimicrobials. The international dimension of TRAINAU is ensured through the strong networks of the host group with European universities, research institutions as well as with international organisations. Fellows will establish links across Europe, stimulating future international collaborations and producing positive effects on their future careers.

TRAINAU contributes to coordination of research training in the area of microbiological risk assessment and enables dissemination of principles and methods for surveillance of antimicrobial usage and resistance to other European countries. TRAINAU also contributes to reinforce the capacity of emerging research groups through enhancing the scientific capacities of the fellows.

Problem:

Non-human use of antimicrobials, in particular the use in food animals, contributes to the public health problems in relation to antimicrobial resistant human infections. Control efforts should be guided by microbial risk assessment in an integrated food chain perspective.

AIMS

TRAINAU’s objectives are to answer the following main questions in order to assess the risks of non-human antimicrobial usage:

- To which extent do different patterns of antimicrobial drug use select for the occurrence of resistant bacteria in animals?
- By which routes and at what rates do resistant bacteria and resistance genes transmit from animals to humans?
- What is the current and potential future public health impact of resistant bacteria and resistance determinants from food animals?

EXPECTED AND OBTAINED RESULTS

The research activities have generated data and developed new methods in order to answer questions that are of crucial importance for conducting risk-based evaluations. The research activities have been focused on specific antimicrobial classes used in animals and the preliminary results are very promising, and by far exceed the expected outcome.

The epidemiological relationships between bacterial isolates from animals, food, and humans have been determined by molecular methods. Resistance genes and the associated mobile genetic elements have been characterised and horizontal transfer between animal and human bacterial populations have been investigated.
The project’s fellows are collaborating on a quantitative risk assessment using their obtained results and the present literature; the outcome of this assessment looks promising but is still under further preparation. A full list of publications directly related to the programme is also available on the website.

Potential applications:
The Early Stage Training programme will strive to continue the activities in a postdoc-based EU research programme.

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TARGETING REPLICATION AND INTEGRATION OF HIV

BACKGROUND
TRIoH developed several novel compounds targeting HIV entry, nucleocapsid, RT or integrase. The discovery of LEDGF/p75 as a major novel target for HIV drug discovery is one of the most exciting new directions in HIV molecular virology originating from TRIoH in recent years. This work has received international appraisal and offers excellent options for economic valorisation in the near future.

AIMS
The general objective was to integrate the various research efforts from different European partners on novel anti-HIV molecules targeting viral replication and integration.

OBTAINED RESULTS
The results obtained by TRIoH include the following.

- Optimisation and use of a multi-parametric assay for entry/fusion was successful to identify new compounds against virus attachment, interaction with CD4, HIV co-receptors, gp41-dependent fusion and HIV-envelope-induced cell-death.
- Optimisation and use of new NC assays have been successful in identifying compounds with anti-NC activity in vitro. Some hits show anti-HIV activity in a multiple round replication assay.

Potential applications:
- Scientific publications in peer-reviewed journals and presentations at international meetings;
- A website for communication with the scientific community and general public;
- An initiative towards AIDS in developing countries;
- The creation of
- The TRIoH training programme was established to organized practical trainings, theoretical classes and a yearly symposium for young researchers within TRIoH and African and Indian students, including the funding of a young researcher special award.

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- EC contribution: €11 610 500
- Duration: 36 months + 6 months extension
- Type: Specific Targeted Research Project
- Starting date: 1 January 2004

http://www.u-psud.fr/

BACKGROUND
In China, a large fraction of the population is infected by Mycobacterium tuberculosis (MTB), the bacteria responsible for tuberculosis (TB), with 500 000 new cases reported each year. A significant proportion of strains is resistant to multiple drugs used to treat this disease. The attenuated Mycobacterium bovis Bacillus Calmette Guerin (BCG) is the only available vaccine against TB, but it does not provide consistent protection.

Tuberculosis China investigated MTB genetic diversity in China (analysis of 6 000 strains from 31 provinces). The goal was to characterise the dominant bacterial populations in China and to ascertain whether the dispersion of the Beijing type is of clonal origin.

This work was the subject of Wan Kanglin’s PhD thesis (Université Paris-Sud, 8 October 2008) under the co-supervision of Dr G. Vergnaud and Prof. Xu Jianguo.

Problem:
A third of the world’s population, mostly in poor countries, is currently latently infected by MTB. The extensive use of the BCG vaccine has not led to eradication of this disease; on the contrary, it may have allowed some strains to emerge, especially in countries where the use of drugs was inadequate. In China, a particular strain family called the ‘Beijing family’ has been found to predominate (van Soolingen et al., 1995).

AIMS
The objectives of the Tuberculosis China project were to help identify emerging MTB strains in order to determine their antigenic characteristics and develop a new protective vaccine, and to understand how MTB strains vary and adapt to new treatments or vaccines. This was an ambitious project necessitating serious organisation and a long-term follow-up.

OBTAINED RESULTS
The consortium obtained the following results:

- genetic diversity of MTB strains, allowing a description of prominent bacterial families and their distribution in China (Figure 1);
- role of BCG vaccination in emergence of new TB strains;
- multidrug-resistance (MDR) strains, potentially triggered by the inadequate use of antibiotics.

Potential applications:
Studies are being performed in Beijing to identify MTB antigens and epitopes for new protective vaccines and specific diagnostic reagents. Immunogenicity and protective capacity may be increased by adding to the BCG strains antigens that induce a T-cell response (Pym et al., 2003).

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UNIFORMITY IN TESTING AND MONITORING HIV RESISTANCE

BACKGROUND
Antiretroviral drugs are increasingly being provided to patients living with the human immunodeficiency virus (HIV) in developing countries. Experience gained in Europe and North America has shown that the use of these drugs dramatically reduced mortality but is also associated with the emergence of drug-resistant HIV.

The EU-funded ‘Strategy to Control Spread of HIV Drug Resistance’ (SPREAD) network gained a leading role in the area of surveillance of HIV drug resistance. Within UNITE-MORE, SPREAD closely cooperated with the World Health Organization (WHO) to support the establishment of a uniform global network for HIV drug resistance surveillance.

UNITE-MORE actively contributed to the further development, transfer and take-up of the SPREAD clinical laboratory guidelines and systems at global level. It also contributed to the objectives of the European Research Area (ERA), increased networking at global level and raising the scientific and technological profile of Europe.

Problem:
If the further spread of HIV drug resistance is not controlled, the fight against the acquired immune deficiency syndrome (AIDS) pandemic could be seriously hampered.

AIMS
UNITE-MORE aimed to support the establishment of a uniform global network for HIV drug resistance surveillance, including standardised laboratory procedures and quality assurance programmes.

EXPECTED RESULTS
support of the establishment of a uniform global network for HIV drug resistance surveillance, UNITE-MORE standardised laboratory procedures and quality assurance programmes.

UNITE-MORE will act as a key force in global efforts on HIV drug resistance surveillance using existing European activities under SPREAD, and the WHO Global HIV Drug Resistance programme within the ‘3 by 5 initiative’ as a strong and solid basis. In addition, UNITE-MORE will contribute to the dissemination of knowledge across countries in four continents.

Potential applications:
The surveillance network could provide governments, scientists and policymakers with relevant and comparable global data on the prevalence, transmission and trends of HIV drug resistance. It could provide a resource for addressing key questions of HIV drug-resistance patterns and spread related to HIV genetic diversity.

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EUROPEAN VIGILANCE NETWORK FOR THE MANAGEMENT OF ANTIVIRAL DRUG RESISTANCE

http://www.virgil-net.org

BACKGROUND
VIRGIL was the first European surveillance network capable of addressing current and emerging antiviral drugs resistance developments in the field of influenza and viral hepatitis. VIRGIL sought to integrate the fragmented European capacities and major expertise in the field into a single coherent Network of Excellence.

Problem:
The high frequency of drug resistance, which may be due to the patient (host), the virus or a combination of both, is a consequence of the successful development of new antiviral therapies in recent decades.

AIMS
The primary goal was to gradually integrate resources and skills dispersed throughout Europe to achieve common research objectives, including the study of the socioeconomic dimension of antiviral drug resistance.

EXPECTED AND OBTAINED RESULTS
The preliminary results obtained on antiviral drugs used to treat influenza and hepatitis B and C demonstrate the pioneer role in Europe of an integrated approach linking basic research and clinical research.

VIRGIL teams were the first to precisely characterise resistances to newly marketed antiviral drugs (adefovir, entecavir and multi resistant strains) for the treatment of hepatitis B. As a result of the links forged between VIRGIL and scientific societies such as EASL (European Association for the Study of the Liver), these results could be adopted by health authorities for the establishment of official guidelines.

In the case of hepatitis C, several in vitro studies identified synergies and antagonisms between antiviral molecules, new more effective interferons, as well as new viral targets for treatments.

A number of standardised criteria for data collection in clinical trials have been established allowing for a comparison of the results obtained in various trials.

Several clinical trials have been initiated on these databases by VIRGIL to characterise resistances of HBV to new molecules such as entecavir or tenofovir, and resistances of HCV to dual therapy with peg-interferon and ribavirin.

VIRGIL plans to develop centralised clinical trial services with major pharmaceutical groups and promote the integration of SMEs (biotechs) in the European economic tissue by linking them with various regions of excellence represented by VIRGIL’s partners.

Potential applications:
The skills and infrastructures developed in the context of this programme could be mobilised in the event of an influenza pandemic. All EU Member States have existing stocks of oseltamivir. These drugs will only be useful if they are used rationally, and if the emergence of resistant viral strains is controlled by continuous surveillance set up throughout the EU according to a sufficiently dense network.
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A VIRTUAL LAB FOR DECISION SUPPORT IN VIRAL DISEASES TREATMENT

BACKGROUND
ViroLab offers a unique opportunity as a blueprint for the many potential diseases where genetic information will become important in future years. The virtual laboratory supports tools for statistical analysis, visualisation, modelling and simulation to predict the temporal virological and immunological response of viruses with complex mutation patterns to drug therapy.

AIMS
The main objectives of ViroLab included:

- a virtual organisation that binds the various components of ViroLab;
- a virtual laboratory infrastructure for transparent workflow, data access, experimental execution and collaboration support;
- epidemiological validation and dissemination of results to stakeholders.

EXPECTED RESULTS
The collaborative research will result in a virtual laboratory for decision support in infectious diseases treatment. New, valuable clinical data and information on treatment of HIV-infected persons will emerge, providing essential insights into the prevalence of drug resistance patterns in treated individuals on a continuous basis. It is of crucial importance for future development of new drugs effective against drug-resistant HIV.

Potential applications:
ViroLab will reliably predict drug susceptibility and virological response, and provide researchers with a support environment to study trends at HIV resistance on individual and population (epidemiological) levels.

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VITAMIN BIOSYNTHESIS AS A TARGET FOR ANTIMALARIAL THERAPY

http://www.hyg.uni-heidelberg.de/vitbiomal

BACKGROUND
Plasmodium falciparum infections place a tremendous burden on global health, which is becoming increasingly aggravated by the worrying rise in P. falciparum drug resistance, making the discovery of novel intervention strategies imperative. The VITBIOMAL project explored the inhibition of a recently identified parasite vitamin biosynthesis pathway as a therapeutic strategy and assessed its potential as drug target.

Problem:
With 300–500 million clinical cases and 1–3 million deaths a year, malaria is one of the most fatal tropical diseases; there is an urgent need to develop and pursue new therapeutic strategies.

AIMS
The aim of VITBIOMAL was to specifically assess vitamin B₆ de novo biosynthesis of Plasmodium as a target for antimalarial drug development.

OBTAINED RESULTS
The results obtained by VITBIOMAL include:

- generation of knockout parasites of the Pdx1 (vitamin B₆ biosynthesis) and of the pdxK gene (vitamin B6 uptake/salvage) in the mouse malaria model system;
- growth delay of the erythrocytic forms;
- massive reduction of sporozoite numbers ranging from 90 (Pdx1 knockout) to 99% (pdxK knockout);
- depletion of B6 vitamers from the growth medium had no effect on the development of P. falciparum blood stage forms, indicating that vitamin B6 biosynthesis is sufficient to cover the needs of pyridoxal 5-phosphate;
- determination of structures: Pdx2 from P. falciparum (1.6 Å), Pdx1 from Bacillus subtilis (to 2.0 Å), Pdx2 from B. subtilis in free (1.7 Å) and inhibitor-complexed state (2.2 Å) and the ternary complex of B. subtilis Pdx1:Pdx2 with substrate glutamine (2.1 Å) (3, 6);
- construction and testing of a homology model of the plasmodial PLP synthase.

Potential applications:
The partners envision antimalarial and possibly antiapicomplexan and/or antibacterial drug development.

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Project number: LSHP-CT-2005-012158 ■ EC contribution: €1 000 000 ■ Duration: 24 months ■ Type: Specific Targeted Research Project ■ Starting date: 1 June 2005
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