Project no.512155

GenOSept

Genetics of Sepsis and Septic shock in Europe

Instrument: STREP

Thematic Priority: Fundamental knowledge and basic tools for functional genomics in all organisms

Publishable Final Activity Report

Period covered: 1st January 2008 to 31 Dec 2008 Date of preparation: February 2009

Start date of project: 1st January 2005 Duration: 48 months

Project coordinator name: Frank Stüber and Nathalie Mathy

Project coordinator organisation name: ESICM

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1. Project Execution

1.1.Project abstract

GenOSept is a specific targeted research project (STREP) which uses a multidisciplinary fundamental genomics approach (gene expression, structural genomics, and population genetics) to examine genetic predisposition to sepsis.

Sepsis (life-threatening infection) is a major public health problem throughout Europe. In the USA in 1995 it cost $17 billion to treat 751,000 patients with severe sepsis, of whom 28.6% died. The Centre for Disease Control suggests that sepsis-attributable mortality rates are rising. We hypothesize that susceptibility to expensive new treatments, and fatal outcomes from severe sepsis, are in part, genetically determined.

GenOSept work packages will test this hypothesis using the following approach. We will use gene expression studies to define novel candidate genes including those controlling programmed cell death. The novel candidate genes so identified will then be analysed in subsequent epidemiologic studies of genetic predisposition to sepsis-related mortality and morbidity in European intensive care units. The European Society of Intensive Care Medicine (ESICM) will co-ordinate a consortium of leading experts in sepsis, genomics, genetic epidemiology, biometrics and genetic high-throughput genotyping to link this new science to patient-centred outcomes.

GenOSept will provide important data on gender-related mortality and morbidity. It will have a major impact on diagnosis and treatment of European sepsis patients in subsequent therapeutic trials by targeting risk subpopulations and focussing expensive new treatments. GenOSept will standardise protocols for genotyping, facilitate application of new knowledge in functional and structural genomics, harmonize high-throughput genotyping and quality control between major European centres, and contribute to reducing sepsis-related mortality in European health care.

1.2.Project objectives

The GenOSept project links European intensive care clinicians with laboratory scientists to improve our understanding of how genetics affect our patients' outcome from severe sepsis and septic shock.

Genetic predisposition for the incidence and outcome of sepsis has been recognized and suggested as possible powerful tool for future risk stratification and even as a determinant of treatment options and randomisation in clinical trials. GenOSept also contains a module which links patterns gene expression with patterns of genomic variation in corresponding genes and proteonomics.

Genomic variants may influence the individual phenotype including gene expression levels and patterns as well as protein levels and protein structure. As possible result, future intensive care physicians may have access to readily available genetic risk patterns including

pharmacogenetics of their patients which not only allows for better risk stratification, but may also help tailor individual patient care and drug therapy.

Major milestones for the GenOSept project were:

- Consensus definitions and setting up of an inclusion and exclusion criteria database
- Collection of blood samples from some 2500 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 ICUs
- Definition of a diagnostic SNP set to identify patients at risk of dying from sepsis

The project has the following expected results:

- GenOSept is a multidisciplinary fundamental genomics approach (gene expression, structural genomics, and population genetics) and will contribute to unravel genetic predisposition of Sepsis.
- GenOSept will define novel candidate genes by gene expression studies. This will include genes directing pathways of the host immune response to infection and inflammation and of programmed cell death. The novel genes identified by expression studies will add to a set of candidate genes used in a subsequent epidemiologic study: The study will deliver data on gender related mortality and morbidity and will have a major impact on diagnosis and treatment of European sepsis patients in subsequent therapeutic trials by targeting risk subpopulations.
- GenOSept will standardise protocols for genotyping to facilitate application of new knowledge in functional and structural genomics.
- It will harmonize standards for European high throughput genotyping and quality control by co-ordinating major European genotyping centres.

1.3.Contractors involved

Part n°.	Participant name	Participant short name	Country	Lead investigator
1	European Society of Intensive Care Medicine	ESICM	Belgium	Julian Bion and Nathalie Mathy
2	Rheinische Friedrich-Wilhelms-Universität Bonn	Universität Bonn	Germany	Frank Stüber
3	Institut Cochin/INSERM	Institut Cochin	France	Jean-Daniel Chiche
4	Chancellor, Masters and Scholars of the university of Oxford	Oxford	United Kingdom	Adrian Hill and Paul Holloway
5	Universita degli Studi di Torino	Universita Torino	Italy	Marco Ranieri and Paolo Cotogni
6	University Rovira & Virgili - Hospital Universitari Joan XXIII	Tarragona	Spain	Jordi Rello
7	Helmholtz Zentrum München	HZM	Germany	Thomas Meitinger
8	Hadassah Medical Organisation	HMO / Hadassah	Israel	Yoram Weiss

9	SIRS-Lab GmbH	SIRS-Lab	Germany	Stefan Russwurm
10	University Ulm, Medical Faculty	UUlmMF	Germany	Marion Schneider
11	Klinikum der Friedrich-Schiller-Universität Jena	University of Jena	Germany	Konrad Reinhardt and Frank Bloos
12	Masaryk University Brno, Medical faculty	Masaryk University	Czech Republic	Vladimir Sramek
13	National Medical Centre	NMC	Hungary	Ilona Bobek
14	Tartu University Clinics	Tartu Clinics	Estonia	Silver Sarapuu

1.4.Coordinator contact details

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Contact person: Nathalie Mathy

1.5.Results achieved to date

During the four reporting periods, the consortium achieved the following:

- Developed electronic Case Report Forms (eCRFs)
- Engaged national coordinators in their role in helping their local ICUs recruit patients for the study
- Obtained ethics approval for ICUs in Europe & Israel enrolled in the study
- Recruited more than 2500 patient Europe-wide (and Israel) for genome wide genotyping
- Verified the quality and content of the eCRFs for each patient by the quality control team
- Processed blood samples for genotyping
- Evaluated candidate genes and markers suitable for genotyping relative to sepsis
- Evaluated genotyping tests
- Evaluated study designs for the genotyping
- Performed a scientific and statistical analysis of the first step of genotyping and association of the genetic variants with the primary study endpoint: mortality
- Performed a statistical analysis of genotype vs phenotype of patients
- Promoted genomic research in Eastern European countries

1.6.Expected end of project results

By the end of the GenOSept project the following results were achieved:

- Development of a generic electronic case report form to be used for future research projects in intensive care
- Completion of the first step of a two step study designed of a genetic epidemiologic study regarding genetic predisposition to sepsis
- Bridging the gap for a genomics and intensive care network of excellence
- Harmonization of standards for European throughput in genotyping and quality control

1.7.Intentions for use and impact

Sepsis is currently a major European public health issue. GenOSept findings contributes to reduce sepsis-mortality and morbidity in European ICUs as risk populations will be defined better. By gathering many investigators and recruiting up to 250 ICUs from all over Europe, GenOSept helps to identify the gaps between the different healthcare systems and especially between intensive care units. The ICU profile survey has allowed us to identify potential variations in organisational structures.
GenOSept will encourage dissemination and harmonisation of standards operational procedures related to intensive care. GenOSept also promotes the setting up of a platform for genomic research in sepsis and Intensive Care in general in Eastern European Countries.

GenOSept links fundamental genomics to a prominent medical problem in European intensive care in a timely manner. Application of gene expression studies and structural genome analysis detecting genomic variation will generate novel data on relevant genes as well as novel genomic variations involved in the genetic predisposition of incidence and outcome from sepsis. The evaluation and use of novel techniques including the gene chip technology and in the establishment of a European network of clinical and laboratory groups working in the field of critical care medicine will strengthen European biotech industry.

Genetic information can be used for further medical specialities. It will used to stratify perioperative patients undergoing high risk surgical procedures. The enhancement of scientific knowledge and subsequent improvement in critical care diagnostics and clinical management are of benefit to whole of the European Community.

2. Dissemination and Use

The major paper(s) reporting results from this study will be published in peer-reviewed journals under the collaborative name of the ESICM Critical Care Research Network GenOSept investigators, with responsible authors named, and attributions including participating ICUs named in an appendix. Since the project generated preliminary results, the consortium believes that a repeat experiment should be performed in 2009, which will reinforce the data already generated. Results of the GenOSept project will be published with this complimentary data set. The consortium expects to publish these articles in International, European or National scientific and educational peer-reviewed publications, as appropriate. One of the most appropriate journals would be the peer-reviewed "*Intensive Care Medicine*" (ca.4000 copies printed each month) or Critical Care journals.

Special attention has been given and is given to the promotion of the project, which has been advertised at high-profile Congress and meetings focussing on intensive care medicine, genomics, and sepsis management. The ESICM Annual Congress gathers ca. 5000 delegates per year and offers a lot of dissemination opportunities: oral presentation during sessions on genomics, poster presentation, circulation of material from both the ESICM booth and the ECCRN (European Critical Care Research Network) section. A lot of care will be also taken to disseminate the results of the project, targeting the intensive care community as a whole: doctors, nurses, researchers, professors, universities, national and international societies of intensive care or related fields, and industry. In addition, major results will be made public to the European citizens by utilizing national media via the different national societies of Intensive Care Medicine.

Project's progress has been announced on a regular basis in the ESICM electronic Newsletter, the GenOSept (www.genosept.eu) and ESICM websites (www.esicm.org), as well as presented at international congresses, such as the ESICM annual congress.