DEMANDE DE LABORATOIRES ASSOCIÉS
International laboratory in respiratory epidemiology

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Abstract

International laboratory in respiratory epidemiology

The purpose is to develop an association between groups with a long-term international recognition in the field of respiratory epidemiology in the context of the construction of European laboratories. The proposal is based on three departments from two institutions, two in France and one in Spain which share the same population-based approach for the investigation of respiratory health problems. Interest in environment, biology and genetics is developed through analytical epidemiological research. Committed to public health issues and clinical relevance, they are further concerned by the need of decreasing European fragmentation in research structures. Timeliness of the project relates to the current dynamism of the three groups (creation in 2006 of laboratories both in France (Inserm U780, Villejuif) and in Spain (Creal, Barcelona), recruitment in 2006 of researchers both in France (Inserm U578, Grenoble) and in Spain. The association will provide a sustainable structure for the teams already involved in the Global Allergy and Asthma Network of Excellence (Ga2len) and numerous national and international networks, will increase European competitiveness and the visibility of respiratory epidemiology.

Types of scientific collaboration will depend on current expertise and background, common interest, potential of added value for one or both institutions and scientific priority. Three lines of research with several topics are seen as final targets for collaborations: chronic obstructive respiratory diseases in adults (asthma and chronic obstructive pulmonary diseases), environmental determinants of respiratory health (occupational risks, air pollution, physical activity, diet, contact with animals and indoor exposure), as well as genetic and biological approaches (by a variety of approaches, including biological collection sampling by non invasive methods). In the emerging post genome respiratory epidemiology phase, two priority areas for collaboration have been defined: epidemiological approaches to refine phenotyping in asthma and chronic obstructive pulmonary diseases and the joint study of environmental and genetic factors (gene environment interactions).

A coordination team integrated by one person from each institution (F Kauffmann and JM Antó) is the basis of the organisational structure. For each research topic, a binational team will be in charge. Activities will include regular short visits (senior), several months exchange at the pre doc, post doc and junior level, biannual common internal seminars, common scientific papers favouring career development of junior researchers, organisation of open workshops, development of new projects in priority areas.

Perspectives, depending on substantial support from both institutions on such integrated project may include the establishment of a common laboratory based on binational conventions to further increase European competitiveness in this field of research of major and still increasing public health importance.
Main publications in the last five years of members of each of the respiratory epidemiology teams

Inserm U780 (Épidémiologie et Biostatistique), Villejuif, France


Inserm U578 (Groupe de recherches sur le cancer du poumon), Grenoble, France


IMIM – Creal (Centre de recerca en epidemiologia ambiental), Barcelona, Spain

Participating groups

The association concerns groups of respiratory epidemiology from two institutions (Inserm in Villejuif and in Grenoble, France and a newly established Centre for Research in Environmental Epidemiology (CREAL) in Barcelona, Spain. The main participants are listed below. More details for each group are provided in appendix 2.

Inserm U780 (Epidemiology and Biostatistics), Villejuif, France
National Institute of health and medical research (INSERM) – Paris 11 University
Director Thierry Moreau, DR1 Inserm
Team of Epidemiology in Pneumology and immuno-allergology (PIA)

Francine Kauffmann, DR1 (team leader)
Rachel Nadif, CR1
Jean Maccario, PU
Marie-Pierre Oryszczyn, IR1
Nicole Le Moual, IE2

Inserm U578 (Research group on lung cancer), Grenoble, France
National Institute of health and medical research (INSERM) – Albert Bonniot Institute
Director Christian Brambilla, PU-PH

Isabelle Pin, PH
Valérie Siroux, CR1

IMIM – Creal (Centre for Research in Environmental Epidemiology), Barcelona, Spain
Municipal Institute of Medical Research (IMIM) - Pompeu Fabra University (UPF)
Director Josep Maria Antó, professor of epidemiology and IMIM director

Josep Maria Antó, professor (Director)
Jordi Sunyer, professor (Co-director)
Manolis Kogevinas, professor (Co-director)
Nino Künzli, ICREA research professor
Jan Paul Zock, researcher Institute of Health Carlos III
Judith Garcia-Aymerich, researcher Institute of Health Carlos III
Cristina Villanueva, researcher
Lettre de soutien

En tant que Directeur de l’Unité INSERM 780, j’approuve pleinement le projet d’association de l’Unité avec l’Unité INSERM 578 à Grenoble (Directeur C Brambilla), et le Laboratoire CREAL, IMIM, à Barcelone (Directeur JM Antó) dans le cadre de la mise en place de Laboratoires Mixtes au niveau européen.

Ce projet est porté dans notre Unité par Francine Kauffmann, responsable de l’équipe “Épidémiologie en Pneumologie et Immuno-Allergologie”.

Villejuif, le 5 mai 2006,

Thierry MOREAU
As the Director of INSERM U 578 I fully support the project of association with INSERM U 780 Villejuif (Director: T. Moreau) and CREAL IMIM Barcelona (Director: J.M. Antó) in the context of the construction of European laboratories. Isabelle Pin and Valérie Siroux as members of U 578 will be in charge of the organisational structure.

La Tronche,
May 4th, 2006
Pr Christian BRAMBILLA
IMIM – CREAL (CENTRE FOR RESEARCH IN ENVIRONMENTAL EPIDEMIOLOGY)

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LETTER OF SUPPORT

As the Director of IMIM- CREAL (CENTRE FOR RESEARCH IN ENVIRONMENTAL EPIDEMIOLOGY) I fully support the project of association with INSERM U 780 Villejuif (Director: T. Moreau) and INSERM U 578 (Director: C. Brambilla) in the context of the construction of European Laboratories.

Josep M Antó, as director of IMIM- CREAL will be in charge of the organisational structure.

Barcelona, June 6th 2006

Pr. Josep M Antó

[Signature]
OBJECTIVES AND CONTEXT

Rationale and antecedents

Obstructive lung diseases, asthma and chronic obstructive pulmonary disease (COPD) represent major and increasing public health problems. The incidence of asthma has more than doubled in the last three decades, concerning at least 5% of adults and 10% of children of the general population. COPD is anticipated to become the third cause of mortality worldwide by 2020, and an increasing source of disability\(^1\). Despite the role of risk factors established so far, such as the major role of smoking in COPD, there is insufficient knowledge to prevent the occurrence of obstructive diseases or exacerbations among diseased patients. Classical hypotheses, such as the direct role of inhaled allergens in asthma have been questioned. New hypotheses have been formulated such as the potential protective role of contacts with infectious agents in early life, the deleterious effects of cleaning agents in adult life for asthma\(^2\) as well as the systemic nature of COPD.

The increase in asthma incidence in children has led worldwide to the development of research in the paediatric age range, sometimes by distracting from adult respiratory epidemiology research, at a time in which COPD is also increasing and cohorts with high asthma incidence in childhood have reached adult age. New complexities are now apparent and, contrary to the common belief that risk factors are well established, new challenges have emerged. Life course epidemiology, considering windows of exposure for risk factors, and windows of disease expression over the life span, subtle gene environment interactions and interactions between environmental factors (such as those along the oxidant/antioxidant pathway or controlling the pattern of immune response) become major research approaches\(^3\). Evidence is accumulating that obstructive lung diseases are heterogeneous, both at the phenotypic and at the etiologic levels, which required to be delineated to set up efficient prevention and therapy. Such approaches need high expertise in the assessment of environmental exposures, in phenotypic characterisation, and in analytic strategies. Access to samples of large sizes and of various ages, collaboration with genetic and biological groups are needed to develop post genome respiratory epidemiology\(^4\). The epidemiologic approach is central to disentangle the determinants of disease in the real setting, to understand its etiology and to assess the impact of evolving risk factors on its evolution.

Whereas numerous groups of cardiovascular, perinatal or cancer epidemiology exist throughout Europe, there is still a limited number of groups, generally of small size, conducting epidemiological research with quantitative approaches and an etiological orientation in the respiratory epidemiology domain. Research teams at Inserm and Creal share the same strategic perspective regarding respiratory epidemiology. They are committed to European integration and have been active players in the field, through their participation to the Ga2len network of excellence (Global allergy and asthma European network), international studies (ECRHS, European Community Respiratory Health Survey) or workshop organisation (post genome respiratory epidemiology). They have a strong and internationally recognised expertise in analytical epidemiology. Combining methodological expertise in environmental issues on aspects of public health and clinical importance, they are also in the front line of the development of biological and genetical approaches in respiratory epidemiology. The teams are highly experienced in study design, statistical analysis, method development regarding the assessment of the environment, phenotypic characterization including recent non invasive in situ methods for studying pulmonary inflammation and have strong collaborations with genetic groups. All teams have large experience in networking at the national and international levels.

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Efficient research depends both on **structures** and on **projects**. Projects combining for example two major studies on asthma (ECRHS and EGEA) (Epidemiological study on the genetics and Environment of Asthma) may be a driving force to build new structures. These two studies play a central role for the three groups and both are part of the new European Integrated Project GABRIEL (A multidisciplinary study to identify the genetic and Environmental causes of asthma in the European Community) coordinated by B Cookson (UK), which started in February 2006. As illustrated in figure 1, these studies, by their common aims, similar main methods, different design and specificities constitute a platform to mutually reinforce the approaches, for example by increasing the range in asthma severity or through potential mutual replication in adult asthma genetics.

Fig 1. Links between groups regarding two major surveys on adult asthma

| EGEA - Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy |
| Design : case control and family design (7-70 yr), 5 French cities |
| Follow-up : 12 years |
| Size : 2000 subjects |
| Methods : ECRHS-like + strong genetic and biologic programme |
| Scientific coordination by multidisciplinary (epidemiology, genetics, clinicians) steering committee (chair F Kauffmann Villejuif), logistic coordination second survey : Grenoble |

| ECRHS - European Respiratory Community Health Survey |
| Design : general population (20-44 yr), 15 countries |
| Follow-up : 8 years |
| Size : 15 000 subjects, with 6000 for genetic analyses |
| Methods : questionnaire, lung function, allergy, environment |
| Scientific coordination by steering committee (chaired by P Burney, London) with 3 Spanish members, leaders of working packages (occupation, air pollution, quality of life) |

Building on long-term existing collaborations, potentials of complementarity with added value and **timeliness** justify the proposal. Previous common activities are reported in appendix 1. Both institutions are currently in a positive dynamic phase and the research teams want to take advantage of it to go further. Two of the laboratories, one in Villejuif (U780) and Creal in Spain have been created in 2006. That same year, specialised researchers (junior and senior) have been recruited both in the young respiratory epidemiology team in Grenoble (U578) and in Creal.

**Proposal - aims**

The overall aim is to make significant progress in the field of respiratory epidemiology. As it needs larger research groups and more integrated scientific activities, the purpose is to develop an association between groups of excellence in the field of respiratory epidemiology in the context of the construction of European laboratories. This proposal consists in developing a **stable programme of collaboration between the respiratory groups of CREAL-IMIM, Unit 780 and 578 INSERM**. The collaboration is applied under the figure of Associated Laboratories as a type of Mixed Laboratories.

The specific aims of the **International laboratory in respiratory epidemiology** are two fold:

- To establish a stable collaboration in respiratory epidemiology in order to achieve a better **critical size**, in order to efficiently **develop the field** and attract new researchers in this exciting area.

**To improve** efficiency and competitiveness of research efforts in **terms of specialization**

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7 1283 reexamined by the end of May 2006 - ISO 9001-2000 certification (February 2006) for the Egea2 data collection
(e.g. genetics, air pollution), data availability (e.g. EGEA-physical activity), innovation (e.g. biomarkers).

Strategy of collaboration

The proposed strategy of collaboration between different groups from different institutions in different countries is based on four principles:

1) To develop a global collaborative approach going beyond the usual project by project initiatives. Such global approach should involve the definition of some common research priorities on which the complementary of the different groups and the other advantages of developing a larger structure (i.e. critical mass) can be exploited in contribution to the development of respiratory epidemiology in Europe.

2) To develop a sustainable structure in respiratory epidemiology that can facilitate the development of long-term longitudinal projects by providing an integrated multidisciplinary framework. Establishing durable structures is one major aim of work that already took place in the context of the European network of excellence Ga2len (Global allergy and asthma European network). Both IMIM and Inserm are partners of the Ga2len network. One of the Inserm groups is leading the genetic working package and Creal-IMIM leads the occupation work package in that network. This well illustrates the complementary orientations of both institutions to develop modern respiratory epidemiology taking into account environmental and genetic aspects.

3) To take advantage of mutual strengths. Whereas all groups are highly experienced in respiratory epidemiology, establishment of longitudinal cohorts and analytic strategy, they have specific complementarities such as high experience in environmental exposures assessment in Barcelona as well, but in a lesser extent in Villejuif, high integration with genetic and biological approaches in Villejuif as well but to a lesser extent in Barcelona, high clinical expertise in Grenoble and in a lesser extent in Barcelona, high experience in public health approaches in Barcelona. Whereas most European groups are now running asthma epidemiology programs, there is, contrary to 20 years ago, less expertise in COPD epidemiology and the association of the group in Barcelona and Villejuif will strengthen projects underway in Barcelona and facilitate new developments in that important area.

4) To increase the visibility of the associated laboratories. Respiratory epidemiology is facing new challenges, which requires a major development at the international level. Whereas the Barcelona and Villejuif groups have already been attractive laboratories in the field as shown by the number and quality of visiting senior researchers during sabbatical leave, the needs are much higher. It is essential that respiratory epidemiology becomes an attractive area of research for young epidemiological scientists in Europe and elsewhere. The proposed International laboratory in respiratory epidemiology would be a strong incentive in that area. It is worthy to note that the Barcelona group already organises each year in Florence a specialised summer course on environmental epidemiology with strong focus on respiratory health problems.

In the following sections the scientific programme is presented according to a conceptual framework that has emerged from the previous collaboration background. The common research programme is organized in several lines which are illustrated by various topics conducted by specific researchers on which a degree of collaboration has been already developed or can be easily anticipated. Finally the long-term priorities are defined as a way to secure that the collaboration will have a substantial scientific added value. The organization and working plan is presented to set up various activities starting by short-term ones with a time-plan to structure activities around the defined priorities. In appendices, are presented common activities (till 2005 and in the last 12 months), and a description of the teams including their publications and grants.
SCIENTIFIC PROGRAMME

Framework

The framework of the scientific programme is based on the already existing capacities and projects in both institutions. After a detailed analysis of existing activities three different types of scientific collaboration have been distinguished:

i) Research areas where both institutions have accumulated substantial expertise and background and are of common interest for the future (adult asthma, respiratory allergy and occupational related risks),

ii) Areas of research where there is complementarity for a variety of reasons that can result in added value to one or both institutions (COPD, physical activity, air pollution and diet)

iii) Research areas that are seen as of great potential and interest by both institutions, though current development is still limited either because the state of the art is limited or because insufficient background (gene environment interactions, new biological markers).

Lines of research

The scientific programme of the present proposal is organized in three different lines of research. These three lines include most of current and planned activities in both institutions. Within each of these lines there are several topics that are seen as the final targets for collaboration.

1) Chronic obstructive respiratory diseases in adults: asthma and COPD

Regarding asthma (main persons involved: JMA, JS, CV, FK, VS, IP, ..), efforts have been made to standardize the phenotype in epidemiology and the ECRHS survey has set up a standardized questionnaire now used internationally. Assessing the probability of definite asthma, quantifying its severity and assessing its evolution over time poses new challenges. Methodological work regarding the evolution of asthma, a disease with variable expression is pursued in Barcelona (ECRHS) and extensive work to define various dimensions regarding asthma severity has been conducted in Inserm (EGEA). A continuous score for asthma has been constructed in the ECRHS by the Barcelona group, which could relate to the probability of definite asthma and/or measure asthma severity. It is planned to take into account new measures of asthma related phenotypes including quality of life on one side and new biomarkers (derived from non invasive measures) in order to define robust measures of asthma in general and subphenotypes (allergic and non allergic, mild and severe, persistent and variable, etc). Whether definitions of asthma set up in a clinical setting (EGEA) or for general populations (ECRHS) may be used in the other situation will be assessed. Specific work will be conducted to estimate the incidence, persistence and remission between childhood and adulthood in the EGEA study. Projects may include a third follow-up in the ECRHS survey allowing to study the evolution of asthma in the general population and the occurrence of COPD.

COPD (JMA, JG, FK, RN, RV ..) which has been classically defined through low lung function, has been a long term interest in the group in Villejuif. Recent literature has shown the systemic nature of the disease and the need to incorporate new items in the phenotypic characterization. Low body mass index, exercise capacity and muscle strength are now being used for staging the severity of COPD. Improving phenotypic definition of COPD will be approached by studying nutritional factors in Inserm (Paris area work study, 2 examinations 1960 and 1972, survival data till 2006) and of physical activity in Creal (EFRAM study on COPD patients, Collaboration with Copenhagen city study to assess COPD in a general population). It is planned to assess in Creal the phenotypic heterogeneity of COPD in a new study conducted in COPD patients with numerous physiological and biological markers. Further it is planned to evaluate in the French EGEA study mixed forms between severe asthma and COPD.

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COPD by considering smoking asthmatics with low lung function and to explore the feasibility of setting up a research program on COPD in the large E3N survey\(^9\) as the age range is of particular interest.

2) Environment determinants of respiratory health

**Occupational risks** (MK, JPZ, JMA, NLM, FK, .. ) represent a main cause of asthma and COPD. Occupational asthma is now the first occupational respiratory disease. It is difficult to assess occupational exposures in general populations. Major work has been conducted in Creal and in Inserm regarding methods to assess asthma-specific occupational hazards: designing questionnaires on specific hazards for a number of jobs (such as cleaners, personnel in hospitals etc.), and setting up a job exposure matrix (JEM) to assess exposure to a variety of asthmogens, both methods now used internationally at a large scale. The deleterious effect of cleaning has been evidenced. It is planned to develop research on the methodological aspects such as examining the correlation between the assessments of specific exposures by the various methods (JEM, specific questionnaire), and update the asthma-specific JEM. A new study on cleaners is currently set-up in Spain. Joint analyses of EGEA, ECRHS, and Sapaldia (major Swiss study) will be conducted using the various methods and in particular on the effects of cleaning and disinfectant exposures.

**Air pollution** (NK, JS, ER, FK, IR, .. ) plays a role in various respiratory diseases. It increases overall mortality, is related to COPD and triggers asthma attacks. Its role in the occurrence of asthma is a debated issue. Estimation is extremely difficult, especially for assessing long-term effects. Members of Creal have performed methodological work regarding the estimation and analysis of air pollution effects and have shown its role both on the respiratory and cardiovascular systems. It is planned to evaluate the applicability of exposure assignment by geographical information system in EGEA and ECRHS and to investigate the risk of source specific pollution, in particular traffic related air pollution, on the incidence and course of asthma and COPD.

**Physical activity** (JG, JMA, FK,..) is a new topic of interest in the respiratory epidemiology litterature, which is of great interest from a public health point of view. In Creal, interesting observations regarding the deleterious role of low physical activity in COPD exacerbations have been shown. Contrary to epidemiological surveys in cardiovascular and metabolic diseases, very few studies in the respiratory field have included measurements in physical activities. Such data are available in the EGEA2 survey as well as in the E3N survey. It is planned to develop epidemiological work on physical activity as a full topic to explore its role in a variety of respiratory outcomes. Studies on the effects of physical activity on the incidence and the course of asthma and COPD (asthma incidence, respiratory symptoms, lung function, hospital admissions and respiratory mortality) by studying patient's series and the general population will be conducted. Its effect on asthma incidence will be studied on the E3N cohort, on asthma severity in the EGEA survey and on various COPD related phenotypes in the new Spanish survey (PAC-COPD).

**Diet** (JdB, IR, JG, RV,..) is a relatively new topic in respiratory epidemiology and few studies have included proper assessment methods. There is still no consensus regarding the methods and active research regarding analyses. Both Inserm and Creal have decided a few years ago to enter this field and due to a lack of local expertise have established a collaboration with an international expert in the field (I Romieu, a french researcher working in Mexico and currently on a sabbatical visit in Creal). Food frequency questionnaires adapted for France and Spain have been set up. Young researchers interested in the field are being trained in Creal and Inserm. Results already obtained in the French E3N survey have shown the interest of dietary patterns, a new approach complementing the food and nutrient approaches. It is planned to evaluate the effects of diet on the incidence and the severity of asthma in studies conducted in children in Creal (INMA\(^10\)), in adults in France (E3N and EGEA2 studies, and the exacerbations of COPD in the PAC-COPD study). Studies regarding the

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\(^9\) E3N-asthma survey - Longitudinal survey of women affiliated with MGEN, a health insurance for teachers (coordinated by F Clavel-Chapelon) – conducted in France Objective: Role of nutritional and hormonal factors for various diseases in women (mostly cancers, but also asthma and cardiovascular diseases) Population: 100 000 women, affiliated with MGEN, 40 to 65 years of age. \(^{Start}1990, \text{follow-up} every 2 years (85 000 responses at the 7th questionnaire in 2003, 8th questionnaire underway)\)

\(^{10}\) INMA – Infancia y Medio Ambiente. – Longitudinal survey on development and health from early foetal life until childhood – Spanish Network of Excellence. **Objective**: Role of prenatal exposure and diet on foetal and infant’s growth, health (including allergies) **Population**: 3300 pregnant women and their children. Start birth, follow-up till 4 years of age
interactions between environmental exposures are planned as air pollution, smoking and occupational hazards are a source of oxidants whereas some dietary patterns may be protective. A detailed program will be set up with RV (currently in a post doc in nutrition epidemiology in Harvard), regarding in particular the Egea2 and E3N surveys.

Contact with animals, a particular aspect related to indoor exposure (MPO, JPZ, FK ..), has been advocated as a protective factor for allergy (hygiene hypothesis) and is an active topic of research in Europe. Research is currently conducted in various longitudinal studies in children to assess which specific agent (related to infectious agents) may be responsible of the delayed maturation of the immune system towards a balance between Th1 and Th2 pattern favouring a pro allergic Th2 pattern. A complementary line of research followed at Inserm is to evaluate long-term effects in adulthood which needs to define appropriate assessments of contacts with livestock and pets over the life span. Geographical methods, based on birth place and agricultural census have been set up in France. Protective effects on allergy of living in the country and of early contacts with pets have been shown in adults from the EGEA survey. There are limited information regarding the interaction of various indoor exposures. It is planned to evaluate the role of early exposure to livestock on the age of onset and severity of asthma in the E3N, Paarc11 and EGEA surveys, to assess the role of the amount of exposure to pets and livestock over the lifespan on allergy and respiratory outcomes in EGEA2. Further work to improve exposure assessment possibly through geographical methods applicable in other countries is considered.

3) Genetic determinants and biomarkers.

Research in genetics (MK, NK, JS, JMA, FK, VS, RN, MPO ..) has exploded in the last 10 years in the respiratory field and the Inserm group has taken an important place in the field, by realizing one of the first five genome screens for asthma in the EGEA study. It corresponds to a long term commitment in the field and the establishment of close cooperation with top-level groups in genetics in France (Inserm U794, U535, CNG). Segregation, linkage and now more association studies have been developed in the EGEA study, a major study in the field of respiratory genetics which by its design combining a case control and a family approach is particularly adapted to a variety of analyses. The genetic program of the EGEA study (coordinated by F Demenais, Inserm U794) includes two genome screens, a fine-mapping program by microsatellites and SNPS and an association program on a variety of candidate genes currently underway. It will be complemented soon by a transcriptomic approach. In parallel, the Creal group has developed a program on association studies for asthma in the context of the ECRHS. All groups belong to the Gabriel european IP (a European project on asthma genetics). Creal is part of the Barcelona Biomedical Research Park a new scientific strategic project of the Catalan Government that includes several groups of international reputation on regulatory genomics.

It is planned to study gene by environment interactions in specific pathways. The pathway approach is the specificity of respiratory epidemiology groups working with genetic groups. The collaboration is close between both and some respiratory epidemiologists are already trained in sophisticated genetic analyses (VS). Candidate genes would be chosen in pathways related to COPD and asthma such as oxidative, nitrosative, immune tolerance and inflammatory pathways. For respiratory phenotypes, relevant environmental factors to be studied jointly will be oxidant-rich environment such as smoking or occupational exposure (possibly disinfectants), and traffic related air pollution. Similarly interaction with dietary patterns with high antioxidant intake is of interest. Regarding the association of exposure to livestock and pets with allergic markers and asthma, potential genetic modifiers in the innate immune pathway (in particular controlling T regulatory cells) will be investigated.

Interest in new biomarkers (RN, MPO, FK, JPZ, JG, ..) is currently developed at the international level, but not like genetic approaches despite their potential to improve phenotypic characterisation. Both Inserm and Creal have been among the first to include exhaled breath condensate collections in studies conducted in the last years. Such non invasive methods could allow to assess in situ inflammation, and potentially more sophisticated measures, such as cytokine levels. Work conducted in the context of the Ga2len network suggests that proteomic approaches in EBC

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may be possible. Both Inserm and Creal are developing phenotypic characterisation based on biological measures, in particular in the EGEA2 survey in asthma, in the new PAC-COPD survey on COPD patients and in the study on the respiratory health effects in fishermen participating in clean-up activities of the Prestige oil spill\textsuperscript{12}.

It is planned to develop a coherent program regarding the analysis of exhaled condensate in various settings, to explore the possibilities of proteomic approaches in serum (pilot studies in progress with CNG) and possibly in EBC, to measure enzyme activities, in particular regarding the antioxidant defence, and more generally to develop a greater use of biomarkers in respiratory epidemiology in conjunction with a biological pathway approach and in connection with genetic programs.

**Priorities**

Among the various topics which will contribute to the project, we have identified priority areas where we can focus efforts in a more defined way. They have been chosen due to their timeliness and because they represent areas at the crossing of the expertise of the associated laboratories.

1. **Epidemiological approaches to refine phenotyping in asthma and COPD**

The lack of a valid definition of asthma has been a persistent drawback of clinical and epidemiological respiratory research. Most epidemiological studies on asthma and COPD have relied upon questionnaires, lung function with bronchial hyperresponsiveness and markers of allergy, such as atopy and IgE levels\textsuperscript{13-14}. More recently, phenotypes of interest of great clinical relevance such as asthma severity or COPD exacerbations have been studied through epidemiological approaches and Inserm and Imim have played a pioneer role in this field\textsuperscript{17,18}. In parallel, advances in cellular and molecular medicine have increased the knowledge about the intermediate phenotypes including the characterization of Th1 and Th2 inflammation patterns and remodelling changes in the airways. Molecular phenotyping using non invasive methods such as induced sputum\textsuperscript{19} and exhaled breath condensate are particularly interesting at the epidemiological and clinical levels. Both institutions have been among the first to incorporate such methods in epidemiological studies (EGEA, Prestige). Furthermore, the recent advancement in genomics has projected renewed interest in understanding the phenotypes of asthma and COPD as associations between candidate genes may substantially differ according to which disease definitions or phenotype variants are used.

Both asthma and COPD need reconsideration of their phenotypic characteristics, limits and heterogeneity at the various phases of the diseases over the life span. Improving the epidemiological definition and characterization of chronic bronchial obstructive diseases is a priority. Problems to be faced include the incorporation to epidemiological studies of new biological markers and classical issues like assessing validity, reliability, inter-laboratory comparability. In response to these challenges both groups have recently undertaken large collaborative studies with the group of Inserm focusing on severe asthma (EGEA Study) and the group of Barcelona on COPD (The PAC-COPD study).

\textsuperscript{12} Prestige study - Follow-up study conducted in fishermen who participated to the cleaning and controls, including lung function tests and exhaled breath condensate
\textsuperscript{15} Maccario J, Oryszczyn MP, Charpin D, Kaufmann F. Methodologic aspects of the quantification of skin prick test responses: the EGEA study. J Allergy Clin Immunol 2003;111:750-6
2. Gene environment interactions in asthma and COPD

COPD and asthma are major environmental diseases. The recent increase in asthma is due to environmental changes. Numerous deleterious and protective environmental factors may be risk factors of the disease, trigger of asthma attacks, cause of fatal outbreaks and more generally involved in the evolution of the disease. Not all smokers get COPD. Some effects are of overall low magnitude. Asthma triggers, COPD exacerbations related to environment are observed in subgroups of patients. It is well known that asthma run in families and COPD has a familial component. Extremely active research is going on worldwide regarding asthma genetics and in a markedly less extent for COPD, with a current development based on large-scale association studies, potentially covering the entire genome. Strong genetic methodology has been used mostly by genetically driven groups, with the initial idea of finding a small number of major genes. Now there is a consensus to consider that there are many genes with relatively small effects. Although positional cloning has appeared successful in the field, a lot of observations appear discordant, due to insufficient consideration of phenotype heterogeneity, and population differences. Evidence is accumulating of the extreme complexity of the interactions, in which specific phenotype, environment, genes, and even time (windows of exposure, windows of phenotypic expression) are essential.

Research on joint effects of genes and environmental factors (gene environment "interactions"), although advocated to be central by many groups, is only starting and very few convincing results have been obtained. Respiratory epidemiology is a key domain to explore such aspects due to the strength of the associations with environment. A systemic approach is needed to tackle the underlying complexity. Epidemiology has therefore an essential role to play through its capacity to delineate complex problems, by looking at large populations, and integrative approaches including statistics, clinical aspects, very careful assessment of environment, and analytical strategy not based on a priori defined constructs. The Barcelona group is extremely experienced regarding environment and, in particular for other diseases, has published key findings in gene environment interaction. The group in Villejuif is leading for now 12 years one of the major studies on asthma combining genetic and environmental approaches and has close collaborations with top level groups in genetics.11

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ORGANIZATION AND WORKING PLAN

Organizational structure

We are envisaging a type of structure that avoids both rigidity and hierarchical functioning and promotes participation. A coordination team integrated by one person from each country will be set up (FK,JMA) and will both stimulate and coordinate the process. Specific roles of the coordination team will be: i) planning and monitoring the development of the process, ii) planning and coordinating site visits, iii) dealing with the institutional necessary agreements, iv) looking for funding to facilitate exchange and mobility across groups. As shown in the scientific program, each topic is coordinated by a binational team who takes care of organizing and monitoring the different activities.

Type of activities

Achieving the overall aims will depend on a number of common activities undertaken by the members of the three groups. These activities will include: i) visits of senior researchers to other groups, ii) exchanges of junior and postdoctoral researchers, starting with the "poste vert" from Inserm, iii) co-supervision of doctoral students, iv) common applications to national or European funding, iv) writing common papers.

Time-plan

Three phases have been defined.

1) September 2005 – April 2006: Exploratory/feasibility phase

- Definition of areas of common interests and first strategic plan
- Short term visits and exchanges including mutual invitations to internal meetings of major studies conducted in the other country, namely ECRHS, E3N, EGEA
- Preparation of the first common Inserm-Creal/Ga2len meeting

This phase has been successfully completed (see appendix 1)

The first common meeting held in April 2006 showed the feasibility of the project. Short-term collaborative projects and lines for more ambitious aspects have been defined

2) May- December 2006 : Starting period: exploiting current common interests

In the starting period, common activities will follow the current lines of activities. It is anticipated that it will consolidate the potential of collaboration on a long-term basis, help to define a working research plan focussed on the priorities and set up the conditions for its implementation.

Chronic obstructive respiratory diseases in adults

- Plan a case-case study between EGEA and ECRHS (definition of asthma in longitudinal studies for genetic analyses), involving respiratory epidemiologists and chest physicians
- Develop exchanges regarding COPD epidemiology

Environmental determinants of respiratory health

- Data access to develop physical activity themes (E3N, in collaboration with researchers already involved in nutrition effects on asthma in that study) – starting may 2006
- Estimation of NO2 air pollution exposure in the French EGEA study by the method implemented under the supervision of the Spanish group for the ECRHS with collaboration with researchers in the Netherlands and UK – starting June 2006

- Explore relevance of research future collaborative expansions to understand common pathways of environmental exposure that may lead to respiratory and cardiovascular effects

- Prepare a summary report on approaches to evaluate occupational exposures relevant to asthma and secure access to relevant material on the web

- Plan analyses on various surveys (ECRHSI, Sapaldia and EGEA to examine the determinants of basic questions on occupational exposures that could be used in general asthma studies.

- Plan analyses regarding EGEA2 study for a combined project on nutrition/physical activity/fat free mass in relation to respiratory outcomes – starting June 2006

Genetic and biological approaches

- Explore specific collaborations on biological aspects to assess oxidative and nitrosative stress in blood and exhaled condensate, possibly performing pilot surveys in both countries to be followed by a grant application in 2007

- Organise a meeting on genetic aspects with researchers associated with the genetic programs in France and Spain to explore potentials of collaboration/replication with a special focus on adult asthma genetics – October 2006

Others aspects

- Explore the relevance of a quality management approach (ISO certification-like) in Creal, along lines followed in France in the context of European biological resource centre in asthma – starting June 2006

- Set-up statistical "clinics" – Defining biostatistical problems encountered particularly in Creal to be discussed with a senior biostatistician from Inserm – starting May 2006

- Assess the administrative constraints which may limit the development of the program such as regarding common applications to national grants and find project management help at that administrative level

- Increase language knowledge in Spanish or Catalan at Inserm and in French at Creal (greater need at Inserm for now) to decrease dependence to English in a project based in two Latin countries.

- Evaluate and improve management and coordination -

3) January - December 2007: Developing “de novo” research initiatives based on agreed priorities.

Although this part will largely depend on the success and consolidation of step 2, some of the initiatives that can be anticipated are the following:

- Phenotyping aspects in chronic obstructive respiratory diseases in adults

- Plan common analyses on the ECRHS and EGEA longitudinal studies

- Assess interest and limitations of improving phenotypic (respiratory, potentially lung function) (as well as environmental, in particular regarding cleaning) characterisation in the E3N study, a potential setting for case-cohort studies on severe asthma and COPD
- Environmental determinants of respiratory health and gene environment interactions
  - Develop data analysis regarding cleaning in the E3N study at Inserm in collaboration with researchers from Creal, and evaluate how to develop an overall coherent international program on the risks of cleaning and assess areas for studies on gene environment research in that area.
  - Develop coherent nutrition epidemiological research in respiratory diseases and assess possibilities of studies on gene environment studies in that area.
  - Assess the possibilities of common work regarding gene environment interaction regarding risks associated with early exposure to livestock and pets.

- Other General aspects:
  - Development of analyses with writing of at least 2 common papers
  - Exchanges of researchers (post doc and/or junior and/or senior)
  - Explore exchanges and codirections at the doctoral level
  - Second common Inserm-Creal/Ga2len meeting
  - Explore the need and feasibility of organising a European course in respiratory epidemiology
  - Evaluate and improve management and coordination
  - Explore beyond the current Inserm groups (such as Institut Fédératif de site or research center) and Creal (Imim and Barcelona Biomedical Research Park in Barcelona) the potentials to strengthen the scientific activities of the proposed International laboratory of Respiratory Epidemiology.

Milestones / indicators

Milestones will be 1) the obtention of the Inserm approval and further recognition by other national and international bodies, the efficiency of the management structure, the obtention of appropriate authorizations for data access 2) the publication of the first paper and the obtention of the first grant derived from this proposal 3) the set-up of a common program or major phase of an existing program underway 4) the recruitment of a researcher setting up a binational program.

Indicators will be 1) the number of persons and days spent at the other institution (exchange), 2) the number of shared communications presented to meetings, 3) number of shared papers published in international journals, 4) international workshops organised commonly 5) the number of junior and senior researchers from other countries coming in one of the institutions for a sabbatical period (visibility and attractiveness), 4) the stability and sustainability of research programs, increase in the quality and impact of research.
Appendices
Appendix 1: Common activities

Past common activities 1995-2005

**Seminars**

Antó JM. Occidentalisation : un facteur de risque de l'asthme et des allergies. L'augmentation mondiale de la prévalence de l'asthme a-t-elle été influencée par une augmentation de l'exposition aux rayons ultraviolets ? Séminaire PEPI (pneumo-épidémiologie) - 25 novembre 1997 - Villejuif

Sunyer J. Facteurs de risque de l'asthme chez les adultes jeunes. A propos de l'étude Européenne. ECRHS. Séminaire PEPI - 17 novembre 1998 - Villejuif

**Specialized workshop**
European respiratory Society research seminar
Post genome respiratory epidemiology – January 2002 – Abbaye des Vaux de Cernay
Scientific committee : JM Antó (member), F Kauffmann (chair)

**Teaching**
Sixteenth International Symposium Epidemiology in occupational health (EPICOH), Barcelona, September 2002 - Meet the professor seminar
Kauffmann F. Gene-environment interaction in asthma.

**Common papers**


**Scientific societies responsibilities**
Long range planning committee European respiratory Society
1997-1999 JM Antó (member), F Kauffmann (Chair)
2000-2003 JM Antó (Chair)

**Editorial activities in public health and respiratory journals**
European Respiratory Journal
Associate editors for epidemiology
- Francine Kauffmann 1991-1994
- Josep M Antó 1996-1998
- Jordi Sunyer 1999-present

Occupation and Environmental Epidemiology
Associate editors
- Francine Kauffmann 1994-1996
- Manolis Kogevinas present

Other journals
American Journal of Respiratory and Critical Care Medicine, Associate editor for epidemiology (1994-1999), Francine Kauffmann

**Theses jurys**
- Jordi Sunyer : Valérie Siroux (rapporteur) (2003)
- Manolis Kogevinas : Nicole Le Moual (rapporteur) (2005)
- Francine Kauffmann : Mercès Medinez-Ramon (2005)
Recent common activities 2005-2006

Common Meetings

11 march 2005 – Barcelona
Participants
F Kauffmann, N Le Moual (Villejuif)
JP Zock, JM Antó, M Kogevinas, J Sunyer (Barcelona)
Program
- Ga2len Occupation W.P. Meeting (JP Zock, chair)
- Exchanges with various researchers on occupation and other research topics

6 september 2005 – Barcelona
Participants
F Kauffmann (Villejuif)
JM Antó, M Kogevinas (Barcelona)
Program
Discussion about the project of mixed laboratory

28 november 2005 – Villejuif
Participants
N Le Moual, F Kauffmann (Villejuif)
M Kogevinas (Barcelona)
S Kennedy (Vancouver)
Program
Development of methodological aspects regarding the assessment of occupational exposures

12 january 2006 – Villejuif
Participants
JM Antó, J Garcia-Aymerich (Barcelona)
F Kauffmann, R Nadif, MP Oryszczyn, N Le Moual, R Varraso, E Rage, B Faraldo (Villejuif)
Program
Exchange regarding current research topics regarding asthma and COPD
Discussion about the project of mixed laboratory

13-14 february 2006 – Paris
Participants
M Kogevinas (Barcelona)
F Kauffmann, R Nadif, MP Oryszczyn, C Ravault (Villejuif)
V Siroux (Grenoble)
Program
Ga2len Genetics, genomics and post genomics WP meeting (F Kauffmann, chair)
Towards biological resource center (BRC) on asthma and allergy – potentials and limitations. Exploratory phase regarding quality management aspects in the context of BRC (starting with P Burney, London and M Kogevinas, Barcelona)

15-18 march 2006 – Barcelona
Participants
F Kauffmann (Villejuif)
V Siroux (Grenoble)
JM Antó, M Kogevinas, J Sunyer, N Künzli, JP Zock, J Garcia-Aymerich (Barcelona)
I Romieu (Mexico)
Program
PAC-COPD project: review of progress and discussion about methodological issues
EGEA-ECRHS (studies on asthma): targets for collaboration
Discussion about the project of mixed laboratory – Preparation of the first joint meeting.

23 march 2006 – Villejuif
Participants
J Garcia-Aymerich (Barcelona)
I Romieu (Mexico)
F Kauffmann, N Le Moual, MP Oryszczyn, C Bérard (Villejuif)
V Siroux (Grenoble)
F Clavel (E3N principal investigator), B Leynaert (Inserm U700)
Program
Targets for collaboration and development of the respiratory program (asthma, possibly COPD) in the E3N cohort including aspects regarding physical activity (J Garcia Aymerich), nutrition (I Romieu), severe asthma (V Siroux), hormonal aspects (B Leynaert), cleaning (N Le Moual), livestock exposure (MP Oryszczyn), methodological and organisational aspects.

24-25 April 2006 – Barcelona
First Joint Meeting PIA-INSERM and CREAL-IMIM / GA2LEN
Participants
F Kauffmann, R Nadif, N Le Moual, MP Oryszczyn, E Rage, B Faraldo (Villejuif)
V Siroux (Grenoble)
JM Antó, M Kogevinas, N KüNZli, J Sunyer, JP Zock, J Garcia-Aymerich, others researchers and students
Program including 3 plenary sessions on
a) New biological markers in respiratory epidemiology : exhaled NO and others- chaired by R Nadif (Villejuif) and JP Zock (Barcelona)
b) Phenotypes of asthma : curent limitations and new perspectives – chaired by V Siroux (Grenoble) and J Sunyer (Barcelona)
c) IMIM General seminar: Post genome respiratory epidemiology – F Kauffmann (Villejuif)

2-3 May 2006 – Autrans (near Grenoble)
Annual EGEA seminar
Participants
I Pin, V Siroux, C Pison, J Ferran (Grenoble)
J Garcia-Aymerich (Barcelona)
I Romieu (Mexico)
F Kauffmann, R Nadif, MP Oryszczyn, N Le Moual, E Rage, C Bérard, S Tourmillion-Daurès (Villejuif)
Others participants of the EGEA study (Lyon, Montpellier, Lille, Marseille, Evry Inserm, Evry CNG)
Program
including planification of analyses 2006-2008 on specific topics, with 4 sessions on aspects on already established common interest : phenotypic characterisation of asthma in longitudinal studies (V Siroux, I Pin) ; nutrition (I Romieu/R Varraso), fat free mass (C Pison) and physical activity (J Garcia-Aymerich) ; biological aspects (serum and exhaled air condensate proteomes)(R Nadif, R Matran, I Gut) and genetic aspects (F Demenais, EU IP Gabriel program)

24-26 May 2006 – Barcelona
Epidemiology and biostatistics, workshop organised by C Villanueva, M Benet (Barcelona) and J Maccario (Villejuif)
Participants
J Maccario (Villejuif)
Statisticians M Benet, E Plana, R Garcia, A Amorós, Iserra, G Vellalta
Epidemiologists J Garcia, J Sunyer, JP Zock, M Kogevinas, JM Antó
Program
including (general session) How epidemiologists manage with data and statistical analysis in their projects.
Statistical clinic (discussion with statisticians)

Common teaching
Post conference course - 18th International Symposium on Epidemiology in Occupational Health (EPICOH)
Methodological issues in epidemiological studies in occupational asthma and COPD
EPICOH/Ga2len – Bergen 15 September 2005 – Organised by M Kogevinas (Barcelona), N Pearce (Wellington, New Zealand) – Faculty including JP Zock, F Kauffmann
M Kogevinas : Study designs
JP Zock : Exposure assessment in population and industry based studies
F Kauffmann : Gene environment interactions in asthma

Common paper
Occ Env Med. (in revision)
Meetings planned

Late august/Early september – Villejuif

Participants
M Kogevinas, J Sunyer, N Künzli (Barcelona)
N Le Moual, F Kauffmann, E Rage (Villejuif), others

Preliminary program
Aspects regarding environmental exposures assessments (occupational exposure, air pollution)
Appendix 2: CVs, publications and grants of the three teams
Francine Kauffmann
Tel (33) 1 45 59 50 72
Email : kauffmann@vjf.inserm.fr

born 21 July 1948

Formation
1970 M.S University of Paris, France
1971 AEA (Statistical Methodology) University of Paris, France
1974 MD University of Paris, France

Position
1975 Attachée de recherches Inserm
1981 Chargée de recherches Inserm
1984/5 : Channing Laboratory, Harvard Medical School, Boston
1986 Research Director, second class, Inserm
1999- now : Research Director, first class, Inserm

Leader of the Epidemiology in Pneumology and Immuno-allergology team in Inserm U780 (Unit of Epidemiology and Biostatistics, Director T Moreau)

1994-1999 : Associate Editor, American Journal of Respiratory and Critical Care Medicine
2004- : Working package leader for WP on genetics, genomics and post genomics of the Ga2len (Global allergy and asthma European network) European network of excellence

Themes of research : Epidemiology of respiratory diseases (asthma and COPD) - Genetic and environmental factors

Rachel Nadif
Tel : (33) 1 45 59 51 89
Email : nadif@vjf.inserm.fr

née le 1er novembre 1964

Formation
1986 Maîtrise de physiologie, option animale, Université de Nancy I
1987 DEA Pharmacologie (Métabolisme des médicaments et Pharmacologie clinique), Université Nancy I
1989 DIU Epidémiologie et Recherche Clinique, Université de Reims et Nancy I
1991 Doctorat de l'Université de Nancy I, mention Pharmacologie
1994 Diplôme de Statistiques appliquées à la Médecine, Université Pierre et Marie Curie, Paris VI

Activités professionnelles :
1990-1992 : Attachée Temporaire de l'Enseignement et de la Recherche, Université de Nancy I
1993-1997 : CR2 chargée de recherches INSERM, Unité de recherches en Epidémiologie Santé travail, U420, Vandœuvre-les-Nancy
1998-2001 : CR1 chargée de recherches INSERM, U420, Vandœuvre-les-Nancy
2002- : CR1 chargée de recherches INSERM, Unité d’Épidémiologie et Biostatistique U472 (puis U780), Villejuif

Domaines d'intérêt : Épidémiologie des maladies respiratoires, biologie (en particulier stress oxydant), génétique
Jean Maccario  
Tel (33) 1 45 59 50 16  
Email : maccario@vjf.inserm.fr

né le 1er Août 1942

**Formation**

1966  Licence de Mathématiques - Paris
1968  Pharmacie - Paris V
1971  DEA Analyse Numérique - Paris VI
1978  Doctorat 3° Cycle (Biomécanique) – U.T. Compiègne
1978  Doctorat es Sciences Pharmaceutiques - Paris XI
1979  Agrégation

**Activités professionnelles**

1972 Maître assistant de biomathématiques
1979 Maître de conférences, Limoges
1983 Professeur de 2ème classe, Paris XI
1986 Chercheur associé Inserm U169/ puis 472/ puis 780
1993 Professeur de 1ère classe 2004 - coresponsable M1 Paris 11
1995-2004 Professeur de biomathématiques, Paris 11
1995-2004 responsable du DEA (puis M2) de santé publique
2000 responsable du DU Statistique et Sciences de la vie, Paris 11
2006 Professeur de biomathématiques à Paris 5

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Marie-Pierre Oryszczyn  
Tel : (33) 1 45 59 50 12  
Email : picot@vjf.inserm.fr

née le 17 avril 1946

**Formation**

1968 - BTS Analyse Biologique,
1986 CESAM option épidémiologie,
1995 CESAM option étiologie

**Activités professionnelles**

1984-1991  Assistante Ingénieur, Inserm U169
1991-2000  Ingénieur d'études, Inserm U169 (Dir J Lellouch), puis 472 (Dir T Moreau)
2001-2004  Ingénieur de recherches de deuxième classe, Inserm U472
2005 -     Ingénieur de recherches de 1ère classe, Inserm U472, puis 780

Responsable du groupe de travail "Épidémiologie descriptive et étiologique des marqueurs de l'allergie" de l'étude épidémiologique sur les facteurs génétique et environnementaux de l'asthme (EGEA) depuis 1996
Nicole Le Moual
Tel : (33) 1 45 59 50 70
Email : lemoual@vjf.inserm.fr

née le 26 octobre 1962

Formation
1983 DUT Statistiques/traitement informatique des données, IUT Vannes
1994 DU Statistique et sciences de la vie
2000 DU Toxicologie industrielle
2001 DESS Méthodologie et statistique en recherche biomédicale, Paris XI
2005 - Thèse d'Epidémiologie, Paris XI

Activités professionnelles
1983-1987 Technicienne 2B Inserm
1987-1992 Assistante ingénieur Inserm, Unité 170 (Recherche épidémiologiques et statistiques sur l'environnement et la santé, Dir D Hémon)
1992-2003 Assistante ingénieur Inserm, Unité 169 (Dir J Lellouch), puis Unité 472 (Epidémiologie et Biostatistique, Directeur T Moreau)
2004 - Ingénieur d'Etudes Inserm, Unité 472, puis Unité 780

Responsable du groupe de travail "Risques professionnels" de l'étude épidémiologique des facteurs génétiques et environnementaux de l'asthme (EGEA) depuis 1996

Other members of the group
Estelle Rage, Doctoral student, second year – Thesis on bronchial hyperresponsiveness in asthma
Raphaelle Varraso, post doc currently in Harvard University, Nutrition Department (Dir W Wilett)
Béatrice Faraldo, assistant
Chloé Bérard, statistician

PUBLICATIONS 2000-2006 (RESPIRATORY AND SELECTED OTHERS)

2000

2000; 55: 629 [correspondence]


2001


2002

20. **Kauffmann F**, Oryszczyn MP, **Maccario J**. The protective role of country living on skin prick tests, immunoglobulin E and asthma in adults from the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyper-responsiveness and atopy. Clin Experim Allergy 2002; 32:379-86

2004

45. Le Moual N, Kennedy S, Kauffmann F. Occupational exposures and asthma in 14,000 adults from the general population. Am J Respir Crit Care Med 2004; 160: 1108-1116
2005


2006


GRANTS

2000

ARC (Association de Recherche contre le cancer) 2000
Demandeur: F Kauffmann

2001

Ministère de l'environnement – Programme environnement et santé 2000
Demandeur: F Kauffmann
Montant obtenu: 52 K€
Inserm/Ministère de la Recherche : Cohortes et collections 2001
Demandeur : F Kaufmann : 175 K€

2002
Merck, Sharp and Dohme 2002
Nom du contrat EGEA Second survey
Demande : Inserm (F Kaufmann) et CNG (M Lathrop) avec 2 équipes pour l'Inserm : A Epidémiologie respiratoire (F Kaufmann), B épidémiologie génétique (F Demenais)
Montant obtenu : - 720 K€ ; pour le nouvel examen des sujets (Kaufmann) 170K€ pour l'épidémiologie génétique (Demenais), 314K€ pour la génétique moléculaire (Lathrop)

2003
Agence française de sécurité sanitaire de l'environnement – AFSEE 2003
Nom du contrat : Role of contacts with livestock in asthma- the E3N study
Demandeur : F Kaufmann
Montant obtenu 15K€

Institut de Veille Sanitaire InVS 2003
Nom du contrat : Santé respiratoire et risques professionnels à l’entrée dans la vie active Suivi à 10 ans d’une cohorte de jeunes asthmatiques et de témoins de l’enquête EGEA
Demandeur : F Kaufmann
Montant obtenu : 15 K€

2004
Antadir 2004
Nom du contrat : Etat nutritionnel et mortalité. Une étude longitudinale sur 40 ans chez des travailleurs de la région parisienne.
Demandeur : F Kauffmann (avec C Pison)
Montant obtenu : 15 K€

PHRC régional – Délégation Régionale à la Recherche Clinique d'Île-de-France 2004
Demandeur : P Scheinmann
5 équipes : 1 pneumopédiatrie Necker, (P Scheinmann), 2 pneumopédiatrie Trousseau (A Grimfeld), 3 pneumopédiatrie Grenoble (I Pin, représentant de plus au nom de la coordination logistique nationale les autres investigateurs de Lyon, Marseille et Montpellier), 4 épidémiologie (F Kauffmann), 5 épidémiologie professionnelle (Vancouver, S Kennedy), 6 épidémiologie (Tucson, US, A Wright)
Montant global : 212 768 euros

INSERM-ATC Environnement 2004
Nom du contrat : Gènes candidats à l’interaction avec le stress oxydant et maladies respiratoires chroniques
Demandeur : R Nadif, with S Kleeberger, NIEHS, USA
Montant obtenu : 12 K€

INSERM-ATC Environnement (2004-2007)
Nom du contrat : Ruralité et asthme – Approche interdisciplinaire. Recherche d'indicateurs rétrospectifs de ruralité (4 000 communes françaises) et application à l'étude épidémiologique du rôle protecteur des contacts avec les animaux de ferme dans l'asthme dans l'enquête PAARC (18 000 sujets)
Demandeur : MP Oryszczyn, avec équipe géographes CNRS (N Mathieu) –
Montant obtenu : 20K€

ADEME Agence de l’Environnement et de la Maîtrise de l’Energie
Nom du contrat : Relation de la pollution atmosphérique avec la gravité de dans l’enquête épidémiologique EGEA
Demandeur : F Kauffmann
Montant obtenu : 15 K€

Ga²len Global Allergy and Asthma European Network (EU Network of excellence) (2004-2009)
Coordinator Paul Van Cauwenbergue, Ghent –
WP genetics, genomics and postgenomics (F Kauffmann)
2005

Agence française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET) - Environnement & Santé – Année 2004
Demandeur : F Kauffmann
2 équipes : 1 (F Kauffmann), 2 (I Pin)
Montant obtenu : 100 000 euros

ANR -PSET Agence Nationale de la recherche Programme Santé-environnement et Santé-travail 2005
Nom du contrat : - EGEA -Facteurs environnementaux et interactions gène environnement dans l'asthme et l'allergie
Demandeur : F Kauffmann
3 équipes : 1 ( F Kauffmann), 2 ( F Demenais), 3 (I Pin)
Montant obtenu : 320 000 euros
**INSERM U578, GRENOBLE**

**BRIEF CURRICULUM VITAE OF THE MEMBERS OF THE RESEARCH GROUP ON ASTHMA**

**Isabelle PIN**

Tel : (33) 4 76 76 54 69  
Email : IPin@chu-grenoble.fr

née le 13 janvier 1957

Adresse professionnelle : Inserm U578 (Dir C Brambilla) et Département de Pédiatrie, CHU La Tronche, BP 217, 38043 GRENOBLE Cedex 19

**Titres universitaires**

1984 Diplôme d'Université d'Allergologie et d'Immunologie Clinique (Marseille)  
1985 Doctorat en médecine  
1985 Maîtrise de Biologie Humaine mention Immunologie  
1985 Certificat d'Études Spéciales de Pneumologie  
1989 Certificat d'études Spéciales de Pédiatrie  
1986-1989 Assistant à la Faculté de Médecine de Grenoble.  
1990-1992 Diplôme d'études approfondies de Physiopathologie respiratoire. Faculté de Médecine de Créteil (Université Paris XII).  
2002 Habilitation à Diriger les Recherches : Faculté de Médecine de Grenoble

**Titres hospitaliers**

1989-1991 Assistante de recherche, McMaster University, Hamilton, Ontario, Canada (Pr Hargreave, Pr Dolovich)  
Depuis 1991 Praticien Hospitalier de Pneumologie Infantile au CHU de Grenoble.

**Valérie Siroux**

Tel (33) 4 76 54 95 56  
Email : valerie.siroux@ujf-grenoble.fr

née le 18 décembre 1974

**Formation**

1994 : DUT (Statistique et Traitement Informatique des Données) STID, IUT de Poitiers (86)  
1996 : MST ISASH option Epidémiologie, PARIS V (René DESCARTES).(Maîtrise en Sciences et Techniques en Informatique et Statistique Appliquée aux Sciences de l’Homme)  
1997- : DEA de santé publique, option épidémiologie, PARIS XI  
2003 : Doctorat, Ecole doctorale en épidémiologie, sciences sociales et santé publique, PARIS XI.  
2004 : Cours de statistique appliquée à l'épidémiologie génétique, University of California, Los Angeles.  
2004 : Cours de génétique des populations, University of Arizona, Tucson. Auditeur libre.  
2005 : Méthodes statistiques et utilisation du logiciel FBAT (Familial Based Association Test), Lille. Mars 2005

**Activités professionnelles**

1998 : IPROS (Institut de Prévention et de Recherche sur l'Ostéoporose), CHR Orléans. Epidémiologiste (1 an)  
1999 : Occupational Hygiene Program, Vancouver (Canada). Epidémiologiste (6 mois)  
2004 : Arizona Respiratory Center, Tucson (Arizona), post-doctorat, Pr F. Martinez – Epidémiologie génétique  
2005- Chargée de recherches de 1ère classe, Inserm U578 (Groupe de recherches sur le cancer du poumon, Directeur C Brambilla).  
Thème de recherche : Déterminants environnementaux et génétiques de l'asthme sévère
PUBLICATIONS 2000-2006 (RESPIRATORY AND SELECTED OTHERS)

2000


2001


2002


2003


2004


2005


GRANTS

2000

Demandeur : I Pin

Ministère de l’environnement - Programme santé environnement 2000
Contrat Environnement Santé 2000 N° AC013G
Etude de faisabilité en vue de la réalisation d'une étude longitudinale
Demandeur : F Kauffmann
2 équipes A ( F Kauffmann), B (I Pin)
Montant total obtenu 353 400 francs avec pour équipe B (Pin) : 114 400 francs

2001

Ministère de la Recherche/ Inserm : Cohortes et collections 2001
Demandeur : F Kauffmann
4 équipes I (F Kauffmann), A (F Demenais), B (M Lathrop), C (I Pin)
Obtenu total : 175 000 euros avec pour équipe C (Pin) : 70 000 euros
2002

MERCK 2002
Nom du contrat : Etude EGEA
Demande : Inserm (F Kauffmann) et CNG (M Lathrop), avec 2 équipes pour l'Inserm : A épidémiologie respiratoire (F Kauffmann), B épidémiologie génétique (F Demenais)
Montant obtenu : 720 000 euros pour le nouvel examen des sujets (Kauffmann, incluant l'essentiel du budget de l'examen des sujets coordonné sur le plan logistique à Grenoble par I Pin), 170 000 pour l'épidémiologie génétique (Demenais), 314 000 pour la génétique moléculaire (Lathrop)

2003

Direction de la recherche clinique du CHU de Grenoble 2003
Nom du contrat : Recherche des facteurs génétiques impliqués dans la gravité de l’asthme par criblage du génome
Demandeur : I Pin
montant obtenu: 12 000 €

2004

PHRC régional - Délégation Régionale à la Recherche Clinique d'Ile-de-France 2004
Demandeur : P Scheinmann
5 équipes : 1 pneumopédiatrie Necker, (P Scheinmann), 2 pneumopédiatrie Trousseau (A Grimfeld), 3 pneumopédiatrie Grenoble (I Pin, représentant de plus au nom de la coordination logistique nationale les autres investigateurs de Lyon, Marseille et Montpellier), 4 épidémiologie (F Kauffmann), 5 épidémiologie professionnelle (Vancouver, S Kennedy), 6 épidémiologie (Tucson, US, A Wright)
Montant global : 212 768 euros

Agence française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET, anciennement AFSSE) Environnement & Santé Année 2004
Demandeur : F Kauffmann
2 équipes : 1 (F Kauffmann), 2 (I Pin)
Montant obtenu : 100 000 euros avec pour équipe 2 :40 000)

PHRC régional 2004
Nom du contrat : Gravité de l’asthme et inflammation bronchique dans le suivi de l’étude EGEA
Demandeur : I Pin
Montant obtenu : 31 500 €

2005

Conseil Scientifique AGIRàdom 2005
Nom du contrat : Association entre des polymorphismes génétiques sur ADAM 33 et l’asthme et la sévérité de l’asthme dans l’étude EGEA
Demandeur : I Pin
Montant obtenu: 18 500 €

Conseil scientifique de la Société de Pneumologie de langue Française 2005
Nom du contrat : Sévérité, contrôle, et qualité de vie des asthmatiques dans l’étude EGEA2
Demandeur : I Pin
Montant obtenu : 15 000 €

ANR -PSET Agence Nationale de la recherche Programme Santé-environnement et Santé-travail 2005
Nom du contrat : - EGEA -Facteurs environnementaux et interactions gène environnement dans l'asthme et l'allergie
Demandeur : F Kauffmann
3 équipes : 1 ( F Kauffmann), 2 ( F Demenais), 3 ( I Pin)
Montant obtenu : 320 000 euros avec pour équipe 3 : 100 000
CREAL-IMIM, BARCELONA

BRIEF CURRICULUM VITAE OF THE MEMBERS INVOLVED IN RESPIRATORY EPIDEMIOLOGY

Josep-Maria Antó
Tel : (34) 93 225 75 95
Email : JMAnto@imim.es

Born 17 August 1952
Formation
1975 MD Universitat Autónoma de Barcelona
1979 Specialist in Respiratory Medicine, Universitat Autónoma de Barcelona
1990 PhD, Universitat Autónoma de Barcelona (UAB)

Appointments
1981 Epidemiologist, Municipal Institute of Public Health, Barcelona City Council
1986 Head of the Department of Epidemiological and Environmental Studies, Barcelona City Council
1988 Principal visiting fellow, National Heart and Lung Institute (London, UK; 3 months).
1988 Head of the Dept of Epidemiology & Public Health, Institut Municipal d'Investigacio Medica (IMIM-IMAS)
1996 Head of the Respiratory and Environmental Health Research Unit, IMIM-IMAS
1996 Assistant Professor of Preventive Medicine and Public Health, Department of Medicine, UAB
1998 Professor of Medicine, Department of Experimental and Health Sciences, Universitat Pompeu Fabra
2005 Director of IMIM
2006 Director of CREAL

Awards and editorial activities: Cournant Lecture (European Respiratory Society, 1994)
1991-1995 Associate Editor of the American Journal of Epidemiology
1996-1998 Associate Editor of the European Respiratory Journal

Themes of research: epidemiology of asthma and COPD with special interest on the environmental determinants and prevention of these diseases.

Jordi Sunyer
(34) 93 221 10 09
Email : jsunyer@imim.es

Born 14 October 1957
Training
1980 MD Universitat de Barcelona
1984 Specialist in family medicine
1983-1991 Courses in epidemiology including Diplôme de Statistique appliquée à la médecine, CESAM, Paris, OMS, Brussels, IARC, etc...
1989 PhD Medicine

Appointments
1984 Epidemiologist, Instituto Municipal de la Salud (Council of Barcelona)
1988 Epidemiologist, Dept Epidemiologia y Salud Publica, IMIM
1990 Associate Professor, Salud Publica y Med Preventiva, Universitat Autonoma de Barcelona
1995 Epidemiologist, Unit of Respiratory and Environmental Health research, IMIM
2002 Professor, Experimental Sciences and Health, Universitat Pompeu Fabra (UPF), Barcelona
2006 Codirector, Centre for Research in Environmental Epidemiology, IMIM

(1999-) Associate Editor European respiratory Journal
Member of steering committee of ECRHS

Themes of research: asthma frequency and aetiology - air pollution, occupation and allergy; COPD and air pollution; and effects of persistent pollutants in childhood
Manolis Kogevinas

Tel (34) 93 225 75 68
Email: kogevinas@imim.es

Born 15 February 1956, Greek citizenship

Training
1985 MD, Specialist in radiotherapy
1989 PhD Epidemiology, University of London

Appointments
1989-1994 Epidemiologist, Unit of Analytical Epidemiology, IARC, Lyon, France
1995-2003 Associate professor, Department of Pediatrics, and preventive medicine, UAB, Barcelona
2002-2003 Visiting scholar – Occupational and Environmental Epidemiology Branch, NCI, Bethesda, USA
1994-2005 Respiratory and Environmental Health research Unit, IMIM, Barcelona
2006 Co-Director, Centre for Research in Environmental Epidemiology, IMIM, Barcelona

He is currently also Professor of Epidemiology at the Medical School of Crete, and is Adjunct Investigator at the Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA

Themes of research: Evaluation of environmental and occupational exposures and their interaction with genetic factors. He is also the co-ordinator of large multicentric epidemiological studies on occupational and environmental causes of asthma and studies on bladder cancer and involved in studies on birth cohorts in the EU.

Nino Künzli

Tel (34) 93 221 10 09
Email: kuenzli@imim.es

Born 30 June 1957, Swiss citizenship

Training
1986 MD University of Basel, Switzerland
1993 Master of Public Health, Basel
1995 Specialist Social and Preventive Medicine
1996 PhD University of California Berkely

Appointments
1989-1992 Scientific coordinator of the central epidemiology Unit, Swiss Study on Air pollution and Lung disease in adults (SAPALDIA)
1995-1002 Senior researcher, lnstitute for Social and preventive medicine
2001-2002 Assistant professor, University of Basel
2002-2005 Associate Professor, University of Southern California, Los Angeles
2006 ICREA (Institució Catalana de Recerca i Estudis Avançats) Research Professor

Member of the US National Academy of Sciences Committee on estimating the Health-Risk-reduction benefits of proposed Air pollution regulations, member of US and European advisory and expert committees at the interface of science and policy (WHO, EPA, ..)

Themes of research: Exposure to and chronic main health effects of ambient air pollution
Jan-Paul Zock
Tel (34) 93 221 10 09
Email : JPZock@imim.es

Born 19 August 1996
Dutch citizenship

Training
1990 Msc Programme Environmental Sciences, Wageningen Agricultural University, The Netherlands
1998 PhD Environmental and Occupational Health, Wageningen, The Netherlands

Appointments
2002 Research Fellow, Instituto de Salud Carlos III, Respiratory and Environmental Health research Unit, IMIM

Themes of research : Epidemiology of asthma in relation to occupation and home exposures – Exposure asessement in epidemiology

Judith Garcia-Aymerich
Tel (33) 93 221 10 09
Email : jgarcia@imim.es

Born 29 September 1972

Training
1996 MD Medicine and Surgery, Universitat de Barcelona
2002 PhD Public Health and Methodology on Biomedical research, Universitat Autònoma de Barcelona

Appointments
2005 Research Fellow, Instituto de Salud Carlos III Respiratory and Environmental Health Research Unit,

Themes of research : Respiratory epidemiology : Chronic obstructive pulmonary disease (COPD), course, exacerbation, mortality, hospitalisation, infection, health services utilization, quality of life, physical activity
Environmental epidemiology : air pollution, mortality, hospitalisation, time-series
Born 17 September 1975

**Training**
1998 Degree in Environmental Sciences, Universitat Autònoma de Barcelona (UAB)
1999-2005 Various courses in epidemiology and environmental health
2000 Master in Biological Risk assessment, UAB, Barcelona
2003 PhD Environmental Epidemiology, UAB, Barcelona

**Appointments**
2003-2004 Post Doc Inserm U625, Rennes
2005 Researcher Respiratory and environmental health research Unit, IMIM, Barcelona

**Themes of research:** Environmental epidemiology (water pollution) – Respiratory epidemiology: Asthma, in particular Nutrition (selenium) and asthma (SARI study)

**Other members of the group**
Marta Benet Mora, Statistician
Francesc Castro Giner, PhD Student
Jordi De Batlle Garcia, PhD Student
Raquel Garcia Esteban, Statistician
Benedicte Jaquemin Leonard, PhD Student
Estel Plana Hortoneda, Statistician

**PUBLICATIONS 2000-2006 (RESPIRATORY AND SELECTED OTHERS) 2000**


31. Kunzli N, Ackermann-Liebrich U, Brandli O, Tschopp JM, Schindler C, Leuenberger P. Clinically "small" effects of air pollution on FVC have a large public health impact. Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) - team. Eur Respir J. 2000 Jan;15(1):131-6

2001


46. Sala M, Sunyer J, Herrero C, To-Figuera J, Grimalt JO. Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. Occup Environ Med 2001; 58: 172-177.


57. Sunyer J, Menéndez C. Prenatal risk factors of wheezing at the age of four years in Tanzania (author's reply). Thorax 2001; 56: 897.


2002


2003


2004


121. Antó JM. The causes of asthma: the need to look at the data with different eyes. (editorial). Allergy 2004; 59: 121-123.


2005


146. Pekkanen J, Sunyer J, Antó JM, Burney P, on behalf of the European Community Respiratory Health Study (ECRHS) (....Kogevinas M,...). *Operational definitions of asthma in studies on its aetiology.* Eur Respir J 2005; 26: 28-35.


aerosol particle number concentrations in the five HEAESS cities on the basis of measured air pollution and meteorological variables. Atmos Environ 2005; 39: 2261-2273.


2006


Röösli M, Kunzli N. Commentary: Magnetic field exposure and childhood leukaemia--moving the research agenda forward. Int J Epidemiol 2006; (en Premsa).


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 Networks

Title: Global Allergy and Asthma European Network.
Financing: UE
Period: 2004-2009
Import: 219,000 euros
IP: Manolis Kogevinas

Title: Investigación en epidemiología y salud pública: determinantes, mecanismos, métodos y políticas. Consolidación y extensión de un modelo de investigación cooperativa en epidemiología y salud pública.
Financing: Instituto de Salud Carlos III
Period: 2003-2006
Import: 517,965.64 euros
IP: Josep M. Antó (coordinator)

Title: Infancia y Medio Ambiente (INMA). INMA-Infancia y Medio Ambiente-Barcelona-IMIM.
Financing: Instituto de Salud Carlos III
Period: 2003-2006
Import: 523,953.98 euros
IP: Jordi Sunyer (coordinator)

Title: Bases moleculares y fisiológicas de las enfermedades respiratorias. Implicaciones diagnósticas y terapéuticas. Investigación cooperativa en enfermedades respiratorias.
Financing: Instituto Carlos III
Period: 2003-2006
Import: 106,320 euros
IP: Josep M. Antó and Jordi Sunyer

Projects

Title: Phenotype characterisation and course of chronic obstructive pulmonary disease (COPD): PAC-COPD Study.
Financing: Fundació La Marató de TV3, Fundació Catalana de Pneumologia, SEPAR, Fondo de Investigación Sanitaria,
Import: 184,862 euros
IP: Josep M. Antó (coordinator)

Title: Efecto de la actividad física en la evolución de la enfermedad pulmonar obstructiva crónica (EPOC).
Financing: Fondo de Investigación Sanitaria, SEPAR
Period: 2005-2008
Import: 96,634 euros
IP: Judith Garcia-Aymerich (coordinator)

Title: Integrated Assessment of health risks from environmental stresors in Europe.
Financing: UE
Period: 2005-2010
Import: 55,580 euros
IP: Manolis Kogevinas

Title: Development and application of biomarkers of dietary exposure to genotoxic and immunotoxic chemicals and of biomarkers of early effects, using mother-child birth cohorts and biobanks.
Financing: UE
Period: 2006 – 2011
Import: 321,456 euros
IP: Manolis Kogevinas

Title: Compuestos clorados en piscinas: efectos genotóxicos y respiratorios en niños y adultos jóvenes.
Financing: Ministerio de Educación y Ciencia
Period: 2005-2008
Import: 89,250 euros
IP: Manolis Kogevinas (coordinator)

Title: EaRLy Nutrition programming-long term Efficacy and Safety Trials integrated epidemiological.
Financing: UE
Period: 2005-2010
Import: 271,000 euros
IP: Manolis Kogevinas

Title: Development of Public Health Indicators for Reporting Environmental/Occupational Risks related to Agriculture and Fishery.
Financing: UE
Import: 24,000 euros
IP: Manolis Kogevinas

Title: Environment, genes and asthma: an international study.
Financing: Fundació La Marató de TV3
Import: 119,088 euros
IP: Manolis Kogevinas (coordinator)

Title: PAMCHAR. (Chemical and biological characterisation of ambient air coarse, fine, and ultrafine particles for human health risk assessment in Europe)
Financing: UE
Period: 2002-2005
Import: 30,000 euros
IP: Jordi Sunyer (Researcher)

Title: PHEWE: Assessment & Prevention of Acute Health Effects and Weather Condition.
Financing: UE
Period: 2002-2006
Import: 11,700 euros
IP: Jordi Sunyer (Researcher)

Title: AIRGENE: Air pollution and inflammatory response in myocardial infarction survivors.
Financing: UE
Period: 2002-2005
Import: 173,400 euros

Title: A community based study on occupational asthma, ECRHS-OA.
Financing: Public Health Services
Period: 1999-2002
Import: 248,800 euros

Fellowships

Researcher: Jordi de Batlle
Title: Estudio transversal y de seguimiento de un cohorte de sujetos con EPOC incipiente.
Financing: Fondo de Investigación Sanitaria
Period: 2006-2007
Import: 62,400 euros

Researcher: Judith Garcia-Aymerich
Title: Ayudas para contratos de investigadores del Sistema Nacional de Salud.
Financing: Instituto de Salud Carlos III
Period: 2006-2009
Import: 29,250 euros

Researcher: Nino Kuenzli
Financing: ICREA
Period: 2006-2007

Researcher: Maria Mirabelli
Title: Medical workplace exposures, atopy and asthma in nurses.
Financing: National Institute of Health
Period: 2006-2008
Import: 114,840 euros

Researcher: Joan Fortuny
Title: Ayudas para contratos de formación en investigación para profesionales con formación sanitaria especializada.  
Financing: Instituto de Salud Carlos III  
Period: 2003-2006  
Import: 66,104,64 euros  

Researcher: Jan-Paul Zock  
Title: Ayudas para la cofinanciación de contratos postdoctorales.  
Financing: Instituto de Salud Carlos III  
Period: 2002-2006  
Import: 76,224,82 euros  

Others  
Title: Ajut de Suport als Grups de Recerca de Catalunya (SGR 2005).  
Financial organization: Agència de Gestió d’Ajuts Universitaris de Recerca  
Period: 2005-2008  
Import: 50,000 euros