

DEMANDE DE LABORATOIRES ASSOCIES

International laboratory in respiratory epidemiology

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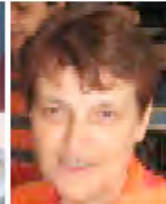
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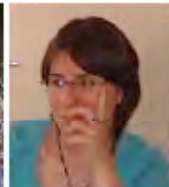
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➤ Abstract

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 (Epidémiologie et Biostatistique), Villejuif, France

1. **Le Moual N**, Siroux V, Pin I, **Kauffmann F**, Kennedy S on behalf of the Epidemiological Study on the genetics and Environment of Asthma (EGEA). Asthma severity and exposure to occupational asthmagens. *Am J Respir Crit Care Med* 2005; 172:440-445
2. Bouzigon E, Dizier MH, Krahenbuhl C, Lemainque A, Annesi-Maesano I, Bétard C, Bousquet J, Charpin D, Gormand F, Guilloud-Bataille M, Just J, **Le Moual N**, **Maccario J**, Matran R, Neukirch F, **Oryszczyn MP**, Paty E, Pin I, Rosenberg-Bourgin M, Vervloet D, **Kauffmann F**, Lathrop M, Demenais F. Clustering patterns of LOD scores for asthma-related phenotypes revealed by a genome-wide screen in 295 French EGEA families. *Hum Mol Genet.* 2004 ;13:3103-13.
3. **Nadif R**, Jedlicka A, Mintz M, Bertrand JP, Kleeberger S, **Kauffmann F**. Role of TNF and LTA polymorphisms on biological markers of response to oxidative stimuli in coal miners: a model of gene-environment interaction. *J Med Gen* 2003 ;40:96-103
4. **Maccario J**, **Oryszczyn MP**, Charpin D, **Kauffmann F**. Methodological aspects in the quantification of skin prick test response. The EGEA study. *J Allergy Clin Immunol* 2003; 111:750-756
5. **Oryszczyn MP**, Annesi-Maesano I, Charpin D, Paty E, **Maccario J**, **Kauffmann F**. Relationships of active and passive smoking to total IgE in adults of EGEA – (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy). *Am J Respir Crit Care Med* 2000 ;161 :1241-1246

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

1. Graves PE, **Siroux V**, Guerra S, Klimecki WT, Martinez FD. Association of atopy and eczema with polymorphisms in T-cell immunoglobulin domain and mucin domain-IL-2-inducible T-cell kinase gene cluster in chromosome 5 q 33. *J Allergy Clin Immunol* 2005 ;116:650-6.
2. Varraso R, **Siroux V**, Maccario J, **Pin I**, Kauffmann F; Epidemiological Study on the Genetics and Environment of Asthma. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005 ;171:334-9.
3. **Siroux V**, Curt F, Oryszczyn MP, Maccario J, Kauffmann F. Role of gender and hormone-related events on IgE, atopy, and eosinophils in the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy. *J Allergy Clin Immunol* 2004;114:491-8
4. **Pin I**, **Siroux V**, Cans C, Kauffmann F, Maccario J, Pison C, Dizier MH. Familial resemblance of asthma severity in the EGEA study. *Am J Respir Crit Care Med* 2002;165:185-9.
5. **Siroux V**, **Pin I**, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J* 2000;15:470-7.

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

1. Chinn S, Jarvis D, Melotti R, Luczynska CM, Ackermann-Liebrich U, **Antó JM**, Cerveri I, de Marco R, Gislason T, Heinrich J, Janson C, **Künzli N**, Leynaert B, Neukirch F, Schouten JP, **Sunyer J**, Svanes C, Vermeire P, Wjst M, Burney P. Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet* 2005; 365: 1629-1635.
2. **Zock JP**, Jarvis D, Luczynska CM, **Sunyer J**, Burney P, on behalf of the European Community Respiratory Health Survey (...**Antó JM**, Soriano JB, Tobías A, **Kogevinas M**,...). Housing characteristics, reported mold exposure, and asthma in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 2002; 110: 285-292
3. **Garcia-Aymerich J**, Monsó E, Marrades RM, Escarrabill J, Félez MA, **Sunyer J**, **Antó JM**, and the EFRAM Investigators (...Alonso J, Barreiro E,...). Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM Study. *Am J Respir Crit Care Med* 2001; 164: 1002-1007.
4. **Sunyer J**, Schwartz J, Tobías A, McFarlane DJ, **Garcia-Aymerich J**, **Antó JM**. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: A case-crossover analysis. *Am J Epidemiol* 2000; 151: 50-56.
5. **Künzli N**, Kaiser R, Medina S, Studnicka M, Chanel O, Filliger P, Herry M, Horak F, Puybonnieux-Texier V, Quenel P, Schneider J, Seethaler R, Vergnaud JC, Sommer H. Public-health impact of outdoor and traffic-related air pollution: a European assessment. *Lancet* 2000; 356 : 795-801

➤ 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

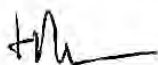
Thierry Moreau
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Lettre de soutien

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 "Epidémiologie en Pneumologie et Immuno-Allergologie".

Villejuif, le 5 mai 2006,



Thierry MOREAU

GROUPE DE RECHERCHE SUR LE CANCER DU POUMON (G.R.C.P.)

Unité INSERM 578

Bases moléculaires de l'initiation et de la progression des cancers du poumon

Directeur

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Letter of support

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





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en epidemiologia
ambiental

IMIM – CREAL (CENTRE FOR RESEARCH IN ENVIRONMENTAL EPIDEMIOLOGY)

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Tlf: 00 34 93 225 7595
e-mail: jmanto@imim.es

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

➤ 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 disability¹. 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 asthma² 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 approaches³. 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 epidemiology⁴. 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.

¹ Murray CJL, Lopez AD. Mortality by cause for eight regions of the world : Global burden of disease study. Lancet 1997;349:1269-1276

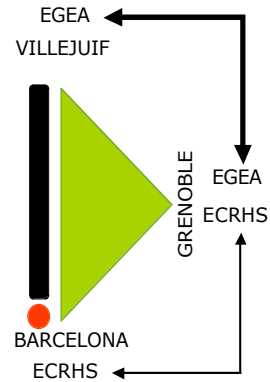
² Zock JP, Kogevinas M, Sunyer J, Jarvis D, Torén K, Antó JM, for the European Community Respiratory Health Survey. Asthma characteristics in cleaning workers, workers in other risk jobs and office workers. Eur Respir J 2002; 20: 679-685

³ Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002 ;31:285-93

⁴ Kauffmann F and the post genome respiratory epidemiology group (J Antó, MP Baur, H Bickeboller, D Clayton, WOC Cookson, D Demenais, PJ Helms, I Humphrey-Smith, S Imbeaud, BM Knoppers, M Lathrop, J Little, N Pearce, D Schaid, E Silverman, S Weiss, M Wjst). Post Genome Respiratory Epidemiology. A multidisciplinary challenge. Europ Respir J 2004 ; 24:471-480

Efficient research depends both on **structures** and on **projects**. Projects combining for example two major studies on asthma (ECRHS⁵ and EGEA⁶ (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

<p>EGEA - Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy</p> <p>Design : case control and family design (7-70 yr), 5 French cities.</p> <p>Follow-up : 12 years⁷</p> <p>Size : 2000 subjects</p> <p>Methods : ECRHS-like + strong genetic and biologic programme.</p> <p>Scientific coordination by multidisciplinary (epidemiology, genetics, clinicians) steering committee (chair F Kauffmann Villejuif), logistic coordination second survey : Grenoble</p>	 <p>http://ifr69.vjf.inserm.fr/~egeanet http://www.ecrhs.org</p>	<p>ECRHS - European Respiratory Community Health Survey</p> <p>Design : general population (20-44 yr), 15 countries</p> <p>Follow-up : 8 years</p> <p>Size : 15 000 subjects, with 6000 for genetic analyses</p> <p>Methods : questionnaire, lung function, allergy, environment</p> <p>Scientific coordination by steering committee (chaired by P Burney, London) with 3 Spanish members, leaders of working packages (occupation, air pollution, quality of life)</p>
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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

⁵ Sunyer J, Basagaña X, Burney P, Antó JM, on behalf of the European Community Respiratory Health Study (ECRHS) (...Soriano JB, Kogevinas M,...). International assessment of the internal consistency of respiratory symptoms. *Am J Respir Crit Care Med* 2000; 162: 930-935.

⁶ Kauffmann F, Dizier MH, Pin I, Paty E, Gormand F, Vervloet D, Bousquet J, Neukirch F, Annesi I, Oryszczyn MP, Lathrop M, Demenais F, Lockhart A, Feingold J. Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) - Phenotype issues. *Am J Respir Crit Care Med* 1997, 156 : S123-S129

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 markers⁸. Further it is planned to evaluate in the French EGEA study mixed forms between severe asthma and

⁸ **PAC-COPD – Phenotype characterization and course of COPD.** Cross-sectional and follow-up study of a cohort of patients with COPD – conducted in Spain. **Objective** : Study phenotype heterogeneity of COPD and assess the relationship of various subphenotypes with disease course. Specific interest in physical activity. **Population** : 350 COPD patients from 10 centres of 3 Spanish regions. **Start** : 2004, yearly examination planned over 5 years.

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 survey⁹ 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 literature, 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 (INMA¹⁰), in adults in France (E3N and EGEA2 studies, and the exacerbations of COPD in the PAC-COPD study) Studies regarding the

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, **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 Tregulatory 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

¹¹ **PAARC – Pollution atmosphérique et Affections Respiratoires Chroniques.** Conducted in 7 cities in France Objective : Long-term effects of air pollution as well as other environmental determinants. Population : 20000 adults 25-59 years from the general population; Start : 1975 (cross-sectional survey) , with mortality data till 2003

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 spill¹².

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 levels¹³⁻¹⁶. 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 field¹⁷⁻¹⁸. 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 sputum¹⁹ 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).

¹² **Prestige study** - Follow-up study conducted in fishermen who participated to the cleaning and controls, including lung function tests and exhaled breath condensate

¹³ Kauffmann F. Genetics of chronic obstructive pulmonary diseases. Searching for their heterogeneity. *Bull Eur Physiopathol Respir* 1984 ;20:163-210.

¹⁴ Sunyer J, Basagana X, Burney P, Anto JM. International assessment of the internal consistency of respiratory symptoms. European Community Respiratory Health Study (ECRHS). *Am J Respir Crit Care Med* 2000;162(3 Pt 1):930-5.

¹⁵ Maccario J, Orszczyn MP, Charpin D, Kauffmann F. Methodologic aspects of the quantification of skin prick test responses: the EGEA study. *J Allergy Clin Immunol* 2003 ;111:750-6

¹⁶ Jaen A, Sunyer J, Basagana X, Chinn S, Zock JP, Anto JM, Burney P; European Community Respiratory Health Survey. Specific sensitization to common allergens and pulmonary function in the European Community Respiratory Health Survey. *Clin Exp Allergy* 2002 ;32:1713-9

¹⁷ Siroux V, Pin I, Orszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J* 2000;15:470-7.

¹⁸ Garcia-Aymerich J, Monsó E, Marrades RM, Escarabill J, Félez MA, Sunyer J, Antó JM, and the EFRAM Investigators. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM Study. *Am J Respir Crit Care Med* 2001; 164: 1002-1007

¹⁹ Pin I, Freitag AP, O'Byrne PM, Girgis-Gabardo A, Watson RM, Dolovich J, Denburg JA, Hargreave FE. Changes in the cellular profile of induced sputum after allergen-induced asthmatic responses. *Am Rev Respir Dis* 1992 ;145:1265-9.

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^{20 21 22}. 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 runs 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 field²³, 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 essential²⁴.

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^{25 26}. 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 interaction²⁷. 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 genetics²⁸.

²⁰ Le Moual N, Siroux V, Pin I, Kauffmann F, Kennedy S on behalf of EGEEA. Asthma severity and exposure to occupational asthmagens. *Am J Respir Crit Care Med* 2005 ;172:440-5

²¹ Anto JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M, Vazquez L. Community outbreaks of asthma associated with inhalation of soybean dust. Toxicoepidemiological Committee. *N Engl J Med*. 1989 ;320:1097-102.

²² Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. *Thorax* 2006 ; 61 : 209-215

²³ Van Eerdekewegh P, *et al.* Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002 ;418:426-30.

²⁴ Martinez FD. Context dependency of markers of disease. *Am J Respir Crit Care Med*. 2000 ;162(2 Pt 2):S56-7

²⁵ Gilliland FD, *et al.* Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med*. 2002;166:457-63

²⁶ Nadif R, Jedlicka A, Mintz M, Bertrand JP, Kleeberger S, Kauffmann F. Role of *TNF* and *LTA* polymorphisms on biological markers of response to oxidative stimuli in coal miners: a model of gene-environment interaction. *J Med Gen* 2003 ;40:96-103

²⁷ Garcia-Closas M, *et al.* *NAT2* slow acetylation, *GSTM1* null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 2005 ;366:649-59

²⁸ Bouzigon E, Dizier MH, Krähenbühl C, Torchard D, Annesi-Maesano I, Betard C, Bousquet J, Charpin D, Gormand F, Guilloud-Bataille M, Just J, Le Moual N, Maccario J, R Matran, Neukirch F, Oryszczyn MP, Paty E, Pin I, Rosenberg-Bourgin M, Vervloet D, Kauffmann F, Lathrop M, Demenais F. Clustering patterns of LOD scores for asthma-related phenotypes revealed by a genome-wide screen in 295 French EGEEA families. *Hum Mol Gen* 2004 ; 13 : 3103-3113

➤ 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

Kauffmann F. Génétique des maladies obstructives. Societat catalana de Pneumologia. Barcelona 20 Février 1997

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

De Cid R, Chomel JC, Lazaro C, Sunyer J, Baudis M, Casals T, Le Moual N, Kitzis A, Feingold J, Antó J, Estivill X, Kauffmann F. CFTR and asthma in the French EGEA study. Eur J Hum Gen 2001 ; 9 : 67-69

Kauffmann F and the post genome respiratory epidemiology group (J Antó, MP Baur, H Bickeboller, D Clayton, WOC Cookson, D Demenais, PJ Helms, I Humphrey-Smith, S Imbeaud, BM Knoppers, M Lathrop, J Little, N Pearce, D Schaid, E Silverman, S Weiss, M Wjst) . Post Genome Respiratory Epidemiology. A multidisciplinary challenge. Europ Respir J 2004 ; 24:471-480

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

American Journal of Epidemiology Associate editor (1991-1995), Thorax, member of the advisory board (1990-1996): Josep M Antó

Theses juries

- Jordi Sunyer : Valérie Siroux (rapporteur) (2003)
- Manolis Kogevinas : Nicole Le Moual (rapporteur) (2005)
- Francine Kauffmann : Judith Garcia Aymerich (2002)
- Francine Kauffmann : Mercedes 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 : current 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 Tournillon-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

Castro-Giner F, Kauffmann F, de Cid R, Kogevinas M. Gene-environment interactions in asthma.

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

INSERM U780, VILLEJUIF

BRIEF CURRICULUM VITAE OF MEMBERS OF THE EPIDEMIOLOGY IN PNEUMOLOGY AND IMMUNOALLERGOLOGY TEAM



Francine Kauffmann

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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

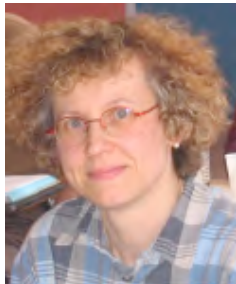
1975 Attachée de recherches Inserm
1981 Chargée de recherches Inserm
1984/5 : Channing Laboratory, Harvard Medical School, Boston
1986 Research Director, second class, Inserm
1999- now : Research Director, first class, Inserm

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
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née le 1^{er} 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'Epidémiologie et Biostatistique U472 (puis U780), Villejuif
Domaines d'intérêt : Epidémiologie des maladies respiratoires, biologie (en particulier stress oxydant), génétique



Jean Maccario

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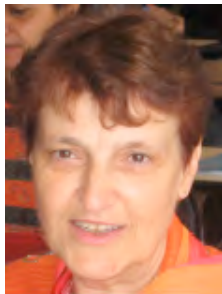
né le 1er Août 1942

Formation

1966 Licence de Mathématiques - Paris
1968 Pharmacien - Paris V
1971 DEA Analyse Numérique - Paris VI
1978 Doctorat 3^e 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 2^eme classe, Paris XI
1986 Chercheur associé Inserm U169/ puis 472/ puis 780
1993 Professeur de 1^{ère} 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



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

1970-1974 Technicienne 3B SC26 Inserm, Paris
1975-1983 Technicienne 2B SC26 Inserm, Paris
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 1^{ère} classe, Inserm U472, puis 780

Responsable du groupe de travail "Epidémiologie 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

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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
Raphaëlle Varraso, post doc currently in Harvard University, Nutrition Department (Dir W Willett)
Béatrice Faraldo, assistant
Chloé Bérard, statistician

PUBLICATIONS 2000-2006 (RESPIRATORY AND SELECTED OTHERS)

2000

1. Sampogna F, Demenais F, Hochez J, **Oryszczyn MP, Maccario J, Kauffmann F**, Feingold J, Dizier MH. Segregation analysis of IgE levels in 335 French families (EGEA) using different strategies to correct for the ascertainment through a correlated trait (asthma). *Genet Epidemiol* 2000 ; 18 :128-142
2. Dizier MH, Besse-Schmittler C, Guilloud-Bataille M, Annesi-Maesano I, Boussaha M, Bousquet J, Charpin D, Degioanni A, Gormand F, Grimfeld A, Hochez J, Hyne G, Lockhart A, Luillier-Lacombe G, Matran R, Meunier F, Neukirch F, Pacheco Y, Parent V, Paty E, Pin I, Pison C, Scheinmann P, Thobie N, Vervloet D, **Kauffmann F**, Feingold J, Lathrop M, Demenais F. Genome screen for asthma and related phenotypes in the French EGEA study. *Am J Respir Crit Care Med* 2000 ;162 :1812-1818
3. Siroux V, Pin I, **Oryszczyn MP, Le Moual N, Kauffmann F**. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Eur Respir J* 2000 ;15 :470-477 .
4. Kennedy SM, **Le Moual N**, Choudat D, **Kauffmann F**. Development of an asthma specific job exposure matrix and its application in the EGEA study. *Occup Environ Med* 2000;57:635-641.
5. **Oryszczyn MP**, Annesi-Maesano I, Charpin D, Paty E, **Maccario J, Kauffmann F**. Relationships of active and passive smoking to total IgE in adults of EGEA - (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy). *Am J Respir Crit Care Med* 2000 ;161 :1241-1246
6. **Kauffmann F, Becklake MR**. Sex and gender. In : *Respiratory epidemiology in Europe*. Annesi-Maesano I, Viegi G, Gulsvik A eds. *Eur Respir Mon* 2000 ; 14 : 288-304
7. **Kauffmann F, Maccario J**. Cross-sectional analyses of longitudinal data and longitudinal analyses of cross-sectional data. In : *Obstructive lung disease: the Nordic experience and future directions*. Eds : A. Gulsvik and E. Omenaas. *Eur Respir Rev* 2000; 10 (75):380-382
8. Becklake MR, **Kauffmann F**. Gender differences in airway behaviour over the human lifespan. *Thorax*

2000 ;55 : 629 [correspondence]

9. **Le Moual N**, Bakke P, Orłowski E, Heederik D, Kromhout H, Kennedy SM, Rijcken B, **Kauffmann F**. Performance of population-specific Job Exposure-Matrices (JEM). European Collaborative Analyses on Occupational risk factors for COPD using Job Exposure Matrices (ECOJEM). *Occup Environ Med* 2000; 57 : 126-132

2001

10. De Cid R, Chomel JC, Lazaro C, Sunyer J, Baudis M, Casals T, **Le Moual N**, Kitzis A, Feingold J, Anto J, Estivill X, **Kauffmann F**. CFTR and asthma in the French EGEA study. *Eur J Hum Gen* 2001 ;9:67-69
11. Zureik M, **Kauffmann F**, Touboul PJ, Courbon D, Ducimetière P. Peak expiratory flow and 4-year occurrence of carotid atherosclerotic plaques. *Arch Int Med* 2001 ;161:1669-76
12. Dizier MH, Besse-Schmittler C, Guilloud-Bataille M, **Kauffmann F**, Clerget-Darpoux F, Demenais F. Indication of linkage and genetic heterogeneity of asthma according to age at onset on chromosome 7q in 107 French EGEA families. *Eur J Hum Gen* 2001 ; 9 : 867-872
13. **Le Moual N**, Bakke P, Kromhout H, Boezen HM, Vermeulen R, Orłowski E, Heederik D, Gulsvik A, Rijcken B, **Kauffmann F**. Relationship between occupational exposure, estimated by two job exposure matrices, and lung function in French, Dutch, and Norwegian community studies. *Eur Respir Rev* 2001; 12 (80):91-97
14. **Nadif R**, **Oryszczyn MP**, Fradier-Dusch M, Hellier G, Bertrand JP, Pham QT, **Kauffmann F**. Cross-sectional and longitudinal study on selenium, glutathione peroxidase, smoking and occupational exposure in coal miners. *Occup Environ Med* 2001 ;58:239-24
15. **Kauffmann F**, Dizier MH, Annesi-Maesano I, Bousquet J, Charpin D, Demenais F, Ecochard D, Feingold J, Gormand F, Grimfeld A, Lathrop M, Matran R, Neukirch F, Paty E, Pin I, Pison C, Scheinmann P, Vervloet D, Lockhart A. Etude épidémiologique des facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) - Protocole et biais de sélection potentiels. *Rev Epidemiol Santé Publique* 2001 ; 49 : 343-356
16. Ravault C, **Kauffmann F**. Validity of the IUATLD (1986) questionnaire in the EGEA study. *Int J Tuberc Lung Dis* 2001 ; 5 : 191-196
17. Baldacci S, Omenaas E, **Oryszczyn MP**. Allergy markers in respiratory epidemiology. *Eur Respir J* 2001;17:773-90.
18. Robert JJ, Gauffeny I, **Maccario J**, Jullien C, Benoit P, Vigne E, Crouzet J, Perricaudet M, Yeh P. Degenerated pIX-IVa2 adenoviral vector sequences lowers reacquisition of the E1 genes during virus amplification in 293 cells. *Gene Ther* 2001 ;8:1713-20.
19. Lacapere JJ, Delavoie F, Li H, Peranzi G, **Maccario J**, Papadopoulos V, Vidic B. Structural and functional study of reconstituted peripheral benzodiazepine receptor. *Biochem Biophys Res Commun* 2001 ;284:536-41.

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
21. Pin I, Siroux V, Cans C, **Kauffmann F**, **Maccario J**, Pison C, Dizier MH. Familial resemblance of asthma severity in the EGEA study. *Am J Respir Crit Care Med* 2002 ; 165:185-89
22. **Kauffmann F**, Annesi-Maesano I, Liard R, Paty E, Faraldo B, Neukirch F, Dizier MH. Construction et validation d'un questionnaire en épidémiologie respiratoire. L'exemple du questionnaire de l'Etude Epidémiologique des facteurs Génétiques et Environnementaux de l'Asthme, l'hyperréactivité bronchique et l'atopie (EGEA). *Rev Mal Respir* 2002; 19 :323-333 .
23. **Kauffmann F**, Dizier MH, **Oryszczyn MP**, **Le Moual N**, Siroux V, Kennedy S, Annesi-Maesano I, Bousquet J, Charpin D, Feingold J, Gormand F, Grimfeld A, Hochez J, Lathrop M, Matran R, Neukirch F, Paty E, Pin I, Demenais F. Etude Epidémiologique sur les facteurs Génétiques et Environnementaux de l'Asthme, l'hyperréactivité bronchique et l'atopie (EGEA) - Premiers résultats d'une étude multidisciplinaire.
24. **Kauffmann F**, Demenais F. Chronic obstructive pulmonary disease. In : King RA, Rotter JI, Motulsky AG eds. The genetic basis of common diseases. New York : Oxford University Press 2002 :155-179
25. **Varraso R**, Massin N, Hery M, Fradier-Dusch M, Michaely JP, Fournier M, Hubert G, Biette P, Rieger B, Berthelin A, Hecht G, **Nadif R**. Not only training but also exposure to chlorinated compounds generates a response to oxidative stimuli in swimmers. *Toxicol Ind Health* 2002 ;18:269-78
26. O'Quigley J, Paoletti X, **Maccario J**. Non-parametric optimal design in dose finding studies. *Biostatistics* 2002 ;3:51-6.
27. Huillard d'Aignaux JN, Cousens SN, **Maccario J**, Costagliola D, Alpers MP, Smith PG, Alperovitch A. The incubation period of kuru. *Epidemiology* 2002 ;13:402-8.
28. Carayol J, Khlaf M, **Maccario J**, Bonaiti-Pellie C. Hereditary non-polyposis colorectal cancer: current risks of colorectal cancer largely overestimated. *J Med Genet* 2002 ;39:335-9.

2003

29. **Oryszczyn MP**, Annesi-Maesano I, Charpin D, **Kauffmann F**. Allergy markers in adults in relation to the timing of pet exposure in the EGEA study. *Allergy* 2003 ; 58:1136-1143
30. Siroux V, **Oryszczyn MP**, Paty E, **Kauffmann F**, Pison C, Vervloet D, Pin I. Relationships of allergic sensitisation, total IgE and blood eosinophils to asthma severity in children of the EGEA Study. *Clin Experim Allergy* 2003 ;33:746-751
31. **Maccario J**, **Oryszczyn MP**, Charpin D, **Kauffmann F**. Methodological aspects in the quantification of skin prick test response. The EGEA study *J Allergy Clin Immunol* 2003; 111:750-756
32. Romieu I, Avenel V, Leynaert B, **Kauffmann F**, Clavel-Chapelon F. Body mass index, change in body silhouette and the risk of asthma in the E3N cohort study. *Am J Epidemiol* 2003 ;158:165-174
33. Molinie F, Favier A, **Kauffmann F**, Berr C. Effects of lipid peroxidation and antioxidant status on peak flow in a population aged 59-71 Y : the EVA study *Resp Med* 2003;97:939-946
34. **Nadif R**, Jedlicka A, Mintz M, Bertrand JP, Kleeberger S, **Kauffmann F**. Role of TNF and LTA polymorphisms on biological markers of response to oxidative stimuli in coal miners: a model of gene-environment interaction. *J Med Gen* 2003 ;40:96-103
35. **Varraso R**, **Oryszczyn MP**, **Kauffmann F**. Sex differences in respiratory symptoms [letter]. *Europ Respir J* 2003;22:716-717
36. Molinié F, **Kauffmann F**. Epidémiologie descriptive. In : Huchon G, Roche N eds. Bronchopneumopathie chronique obstructive. Paris : Margaux Orange 2003, pp 15-34
37. Dellatolas G, De Agostini M, Curt F, Kremin H, Letierce A, **Maccario J**, Lellouch J. Manual skill, hand skill asymmetry, and cognitive performances in young children. *Laterality* 2003 ;8:317-38.
38. Maksimenko A, Malvy C, Lambert G, Bertrand JR, Fattal E, **Maccario J**, Couvreur P. Oligonucleotides targeted against a junction oncogene are made efficient by nanotechnologies. *Pharm Res* 2003 ;20:1565-7.
39. Genty M, Couarraze G, Laversanne R, Degert C, **Maccario J**, Grossiord JL. Complex dispersions of multilamellar vesicles: a promising new carrier for controlled release and protection of encapsulated molecules. *J Control Release* 2003 ;90:119-33.
40. Delavoie F, Li H, Hardwick M, Robert JC, Giatzakis C, Peranzi G, Yao ZX, **Maccario J**, Lacapere JJ, Papadopoulos V. In vivo and in vitro peripheral-type benzodiazepine receptor polymerization: functional significance in drug ligand and cholesterol binding. *Biochemistry* 2003 ;42:4506-19.
41. Petit C, **Maccario J**. A Bayesian analysis of pharmaco-economic data from a clinical trial on schizophrenia. *Stat Med* 2003 ;22:1025-39
42. Letierce A, Tubert-Bitter P, Kramar A, **Maccario J**. Two-treatment comparison based on joint toxicity and efficacy ordered alternatives in cancer trials. *Stat Med* 2003 30;22:859-68

2004

43. Siroux V, Curt F, **Oryszczyn MP**, **Maccario J**, **Kauffmann F**. Role of gender and hormone-related events on IgE, atopy and eosinophils in the EGEA study. *J Allergy Clin Immunol* 2004; 114:491-98
44. Bouzigon E, Dizier MH, Krähenbühl C, Torchard D, Annesi-Maesano I, Bétard C, Bousquet J, Charpin D, Gormand F, Guilloud-Bataille M, Just J, **Le Moual N**, **Maccario J**, R Matran, Neukirch F, **Oryszczyn MP**, Paty E, Pin I, Rosenberg-Bourgin M, Vervloet D, **Kauffmann F**, Lathrop M, Demenais F. Clustering patterns of LOD scores for asthma-related phenotypes revealed by a genome-wide screen in 295 French EGEA families. *Hum Mol Gen* 2004 ;13: 3103-3113
45. **Le Moual N**, Kennedy S, **Kauffmann F**. Occupational exposures and asthma in 14,000 adults from the general population. *Am J Epidemiol* 2004 ; 160 : 1108-1116
46. Siroux V, Pin I, Pison C, **Kauffmann F**. Asthme sévère en population générale : définitions et prévalence. *Rev Mal Respir* 2004 ;21:961-969
47. **Kauffmann F** and the post genome respiratory epidemiology group. Post Genome Respiratory Epidemiology. A multidisciplinary challenge. *Europ Respir J* 2004 ; 24:471-480
48. Siroux V, **Kauffmann F**, Pison C, Pin I. Caractère multidimensionnel de la sévérité de l'asthme dans l'enquête EGEA *Rev Mal Respir* 2004 ;21:917-924
49. Bouzigon E, Chaudru V, Carpentier AS, Dizier MH, **Oryszczyn MP**, **Maccario J**, **Kauffmann F**, Demenais F. Familial correlations and inter-relationships of four asthma-associated quantitative phenotypes in 320 French EGEA families ascertained through asthmatic probands. *Eur J Hum Gen* 2004 ;12:955-63
50. Siroux V, Guilbert P, **Le Moual N**, **Oryszczyn MP**, **Kauffmann F**. Influence of asthma on the validity of reported lifelong environmental tobacco smoke in the EGEA study. *Europ J Epidemiol* 2004 ; 19 : 841-49
51. Annesi-Maesano I, **Oryszczyn MP**, Raheison C, Kopferschmitt C, Pauli G, Taytard A, Tunon de Lara M, Vervloet D, Charpin D. Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? *Clin Exp Allergy* 2004 ;34:1017-23

2005

52. Dizier MH, Bouzigon E, Guilloud-Bataille M, Bétard C, Bousquet J, Charpin D, Gormand F, Hochez J, Just J, Lemainque A, **Le Moual N**, Matran R, Neukirch F, **Oryszczyn MP**, Paty E, Pin I, Vervloet D, **Kauffmann F**, Lathrop M, Demenais F, Annesi-Maesano I. Genome screen in the French EGEA study : detection of linked regions shared or not shared by allergic rhinitis and asthma . *Genes Immun* 2005 ;6:95-102.
53. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F on behalf of the Epidemiological Study on the genetics and Environment of Asthma (EGEA). Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005; 171:334-339
54. **Le Moual N**, Siroux V, Pin I, **Kauffmann F**, Kennedy S on behalf of the Epidemiological Study on the genetics and Environment of Asthma (EGEA). Asthma severity and exposure to occupational asthmagens.
55. Filleul L, Rondeau V, Vandentorren S, **Le Moual N**, Cantagrel A, Annesi-Maesano I, Charpin D, Declercq C, Neukirch F, Paris C, Vervloet D, Brochard P, Tessier JF, **Kauffmann F**, Baldi I. 25-year mortality and air pollution : results from the French PAARC survey. The influence of the assessment of exposure *Occ env Med* 2005 ; 62:543-460.
56. **Nadif R**, Mintz M, Jedlicka A, Bertrand JP, Kleeberger S, **Kauffmann F**. Associations of CAT polymorphisms with catalase activity and exposure to environmental oxidative stimuli. *Free Rad Res* 2005 ; 39 :1345-1350
57. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? *Pediatr Allergy Immunol* 2005 ;16:193-200.
58. Kolopp-Sarda MN, Prin-Mathieu C, Kohler C, Kennel A, Béné MC, Faure G, **Nadif R**. Influence de l'entraînement et de l'exposition aux chloramines sur les réponses immunitaires de nageurs de haut niveau. *Revue Francophone des Laboratoires* 2005 (n° 375), September-October 2005: 37-42
59. Vouriot A, Gauchard GC, Chau N, **Nadif R**, Mur JM, Perrin PP. Chronic exposure to anesthetic gases affects balance control in operating room personnel. *Neurotoxicology* 2005 ;26 :193-198
60. Fourtanier A, Moyal D, **Maccario J**, Compan D, Wolf P, Quehenberger F, Cooper K, Baron E, Halliday G, Poon T, Seed P, Walker SL, Young AR. Measurement of sunscreen immune protection factors in humans: a consensus paper. *J Invest Dermatol* 2005 ;125:403-9
61. Bouzigon E, Demenais F, **Kauffmann F**. Génétique de l'asthme et l'atopie : combien de gènes identifiés ? *Bull Acad Nat Med* 2005; 189:1439-48

2006

62. Wright AL, Stern DA, **Kauffmann F**, Martinez FD. Long term gender differences in the diagnosis and treatment of asthma in childhood : The Tucson Children's respiratory study *Ped Pulmonology* 2006 ; 41 : 318-325
63. **Nadif R**, Mintz M, Rivas-Fuentes S, Jedlicka A, Lavergne E, Roder M, **Kauffmann F**, Combadière C, Kleeberger SR. Polymorphisms in chemokine and chemokine receptor genes and the development of coal workers' pneumoconiosis *Cytokine* 2006 ; 33 : 171-178
64. Romieu I, **Varraso R**, Avenel V, Leynaert B, **Kauffmann F**, Clavel-Chapelon F. Fruit and Vegetable Intakes and Asthma in the E3N study. *Thorax* 2006; 61 : 209-215
65. **Nadif R**, Kleeberger S, **Kauffmann F**. Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use". *Am J Epidemiol* 2006 (sous presse)[letter]

GRANTS

2000

ARC (Association de Recherche contre le cancer) 2000

Nom du contrat Risque attribuable aux expositions professionnelles dans les cancers broncho-pulmonaires.

Etude de la mortalité (1975-2000) dans la cohorte de l'enquête Paarc

Demandeur : F Kauffmann

2001

Ministère de l'environnement – Programme environnement et santé 2000

Nom du contrat : Etude épidémiologique des facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) 1991 – 2001 – Etude de faisabilité en vue de la réalisation d'une étude longitudinale –

Demandeur : F Kauffmann

Montant obtenu : 52 K€

Inserm/Ministère de la Recherche : Cohortes et collections 2001
Nom du contrat : Facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) - Etude longitudinale sur 10 ans : 1991 – 2002
Demandeur : F Kauffmann: 175 K€

2002

Merck, Sharp and Dohme 2002
Nom du contrat EGEA Second survey
Demande : Inserm (F Kauffmann) et CNG (M Lathrop) avec 2 équipes pour l'Inserm : A Epidémiologie respiratoire (F Kauffmann), B épidémiologie génétique (F Demenais)
Montant obtenu : - 720 K€ ; pour le nouvel examen des sujets (Kauffmann), 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 Kauffmann
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 Kauffmann
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'Ile-de-France 2004
Nom du contrat 2004(2004-2006) EGEA : Persistance, rémission, aggravation de l'asthme de l'enfant- Etude longitudinale 1992-2005
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

Nom du contrat : Environnement, asthme, allergie : vers une approche vie entière - Etude épidémiologique des
facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) 1992-2005

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

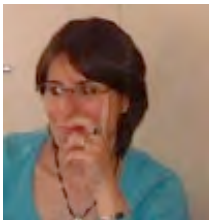
Adresse professionnelle : Inserm U578 (Dir C Brambilla) et Département de Pédiatrie, CHU La Tronche, BP 217, 38043 GRENOBLE Cedex 19

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.
1989-1990 Diplôme du programme "Design, Measurement and Evaluation"
Department of Epidemiology and Biostatistics, MacMaster University, Hamilton, Canada.
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)
2000-2003 : Inserm U472, Villejuif (94) et CHU de Grenoble (38). Epidémiologiste, étudiante en thèse.
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

1. **Siroux V, Pin I**, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J* 2000;15:470-7.
2. **Pin I**, Grenet D, Scheid P, Domblandes P, Stern M, Hubert D. Spécificités de la prise en charge de l'atteinte pulmonaire au cours de la mucoviscidose à l'âge adulte. *Rev Mal Respir.* 2000 Aug;17(3 Pt 2):758-78.
3. Dizier MH, Besse-Schmittler C, Guilloud-Bataille M, Annesi-Maesano I, Boussaha M, Bousquet J, Charpin D, Degioanni A, Gormand F, Grimfeld A, Hochez J, Hyne G, Lockhart A, Luillier-Lacombe M, Matran R, Meunier F, Neukirch F, Pacheco Y, Parent V, Paty E, **Pin I**, Pison C, Scheinmann P, Thobie N, Vervloet D, Kauffmann F, Feingold J, Lathrop M, Demenais F. Genome screen for asthma and related phenotypes in the French EGEA study. *Am J Respir Crit Care Med.* 2000;162(5):1812-8.
4. Le Clainche L, Le Bourgeois M, Fauroux B, Forezza N, Dommergues JP, Desbois JC, Bellon G, Derelle J, Dutau G, Marguet C, **Pin I**, Tillie-Leblond I, Scheinmann P, De Blic J. Long-term outcome of idiopathic pulmonary hemosiderosis in children. *Medicine (Baltimore).* 2000 Sep;79(5):318-26.
5. **Pin I**, Guerin-Develay S, Cans C, Vivier S, Pequegnot C, Lerendu B, Pison C, Paramelle B. Etude transversale de l'intégration scolaire des enfants asthmatiques issus d'un échantillon de la population générale. *Arch Pediatr.* 2000 Aug;7(8):817-24.
6. **Pin I**, McGuigan C, Bost M. Conduite à tenir devant les hémoptysies de l'enfant. *Arch Pediatr.* 2000 Mar;7 Suppl 1:62S-66S.
7. Schwebel C, **Pin I**, Barnoud D, Devouassoux G, Brichon Py, Chaffanjon P, Chavanon O, Sessa C, Blin D, Guignier M, Leverve X, Pison C. Prevalence and consequences of nutritional depletion in lung transplant candidates. *Eur Respir J* 2000 ; 16 : 1050-5.
8. Lespessailles E, **Siroux V**, Poupon S, Andriambeloso N, Pothuau L, Harba R, Benhamou CL. Long-term corticosteroid therapy induces mild changes in trabecular bone texture. *J Bone Miner Res* 2000 ;15:747-53.
9. Lespessailles E, Poupon S, Andriambeloso N, Pothuau L, **Siroux V**, Bouillon S, Benhamou CL. Glucocorticoid-induced osteoporosis: is the bone density decrease the only explanation? *Joint Bone Spine.* 2000;67:119-26.

2001

10. Coltey B, **Pin I**, Ferretti G, Bonadona A, Pison C, Brambilla C. Aspergillose broncho-pulmonaire allergique révélant une mucoviscidose. *Rev Mal Respir* 2001;18:549-51.
11. Devouassoux G, Pison C, Drouet C, **Pin I**, Brambilla C, Brambilla E. Early lung leukocyte infiltration, HLA and adhesion molecule expression predict chronic rejection. *Transpl Immunol* 2001 ;8:229-36.
12. **Pin I**, Bremont F, Clement A, Sardet A. Prise en charge de l'atteinte pulmonaire au cours de la mucoviscidose de l'enfant. *Arch Pediatr* 2001 ;8 Suppl 5:856s-883s.
13. **Pin I**, Pilenko C, Bost M. Place de la mesure non invasive de saturation en oxygène par oxymétrie de pouls dans l'évaluation et la surveillance des bronchiolites. *Arch Pediatr* 2001 ;8 Suppl 1:114S-116S.
14. Benhamou CL, Poupon S, Lespessailles E, Loiseau S, Jennane R, **Siroux V**, Ohley W, Pothuau L. Fractal analysis of radiographic trabecular bone texture and bone mineral density: two complementary parameters related to osteoporotic fractures. *J Bone Miner Res* 2001 ;16:697-704.

2002

15. **Pin I, Siroux V**, Cans C, Kauffmann F, Maccario J, Pison C, Dizier MH. Familial resemblance of asthma severity in the EGEA study. *Am J Respir Crit Care Med* 2002;165:185-9.
16. **Pin I**, Pilenko C, Bost M. [Prevention of respiratory syncytial virus infection by SYNAGIS (palivizumab)] *Allerg Immunol (Paris).* 2002;34:371-4.
17. Devouassoux G, Drouet C, **Pin I**, Brambilla C, Brambilla E, Colle PE, Pison C; Grenoble Lung Transplant Group. Alveolar neutrophilia is a predictor for the bronchiolitis obliterans syndrome, and increases with degree of severity. *Transpl Immunol.* 2002 ;10:303-10.
18. Foucaud P, Borel B, Charara O, Nathanson S, Petitprez P, **Pin I**. Aérosolthérapie antipycyanique dans la mucoviscidose : apport de la tobramycine. *Rev Pneumol Clin.* 2002 Jun;58(3 Pt 1):131-8.
19. Beydon N, Amsellem F, Bellet M, Boule M, Chaussain M, Denjean A, Matran R, **Pin I**, Alberti C, Gaultier C. Pulmonary function tests in preschool children with cystic fibrosis. *Am J Respir Crit Care Med.* 2002;166:1099-104.
20. Gibson PG, Grootendor DC, Henry RL, **Pin I**, Rytala PH, Wark P, Wilson N, Djukanovic R. Sputum induction in children. *Eur Respir J Suppl.* 2002 Sep;37:44s-46s.

21. Pavord ID, Sterk PJ, Hargreave FE, Kips JC, Inman MD, Louis R, Pizzichini MM, Bel EH, **Pin I**, Grootendorst DC, Parameswaran K, Djukanovic R. Clinical applications of assessment of airway inflammation using induced sputum. *Eur Respir J Suppl.* 2002 Sep;37:40s-43s.
22. **Pin I**, Pilenko C, Bost M. Diagnostic différentiel de l'asthme chez le nourrisson et l'enfant. *Arch Pediatr.* 2002;9 Suppl 3:361s-364s.
23. Kauffmann F, Dizier MH, Orszczyn MP, Le Moual N, **Siroux V**, Kennedy S, Annesi-Maesano I, Bousquet J, Charpin D, Feingold J, Gormand F, Grimfeld A, Hochez J, Lathrop M, Matran R, Neukirch F, Paty E, **Pin I**, Demenais F. Etude Epidémiologique sur les facteurs Génétiques et Environnementaux de l'Asthme, l'hyperréactivité bronchique et l'atopie (EGEA) - Premiers résultats d'une étude multidisciplinaire. *Rev Mal Respir* 2002 ;19:63-72 .
24. Zmirou D, Gauvin S, **Pin I**, Momas I, Just J, Sahraoui F, Le Moullec Y, Bremont F, Cassadou S, Albertini M, Lauvergne N, Chiron M, Labbe A; VESTA Investigators. Five epidemiological studies on transport and asthma: objectives, design and descriptive results. *J Expo Anal Environ Epidemiol.* 2002 ;12(3):186-96.

2003

25. **Siroux V**, Orszczyn MP, Paty E, Kauffmann F, Pison C, Vervloet D, **Pin I**. Relationships of allergic sensitization, total immunoglobulin E and blood eosinophils to asthma severity in children of the EGEA Study. *Clin Exp Allergy* 2003 ;33:746-51.
26. **Pin I**, Pilenko C, Gout JP. Perspectives futures dans le traitement de la mucoviscidose. *Arch Pediatr.* 2003 Sep;10 Suppl 2:376s-379s.
27. Wroblewski I, **Pin I**. [Outcomes of children after bronchial foreign body inhalation] *Ann Fr Anesth Reanim.* 2003 Jul;22(7):668-70
28. **Pin I**, Pilenko C, Gout JP, Bost M. Quels prélèvements utiliser pour optimiser l'analyse des sécrétions bronchiques dans la mucoviscidose ? *Rev Mal Respir.* 2003 ;20(2 Pt 2):S63-7.
29. Beydon N, **Pin I**, Matran R, Chaussain M, Boule M, Alain B, Bellet M, Amsellem F, Alberti C, Denjean A, Gaultier C; French Paediatric Programme Hospitalier de Recherche Clinique Group. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med.* 2003 ;168:640-4.

2004

30. **Siroux V**, Guilbert P, Le Moual N, Orszczyn MP, Kauffmann F. Influence of asthma on the validity of reported lifelong environmental tobacco smoke in the EGEA study. *Eur J Epidemiol* 2004;19:841-9.
31. **Siroux V**, Curt F, Orszczyn MP, Maccario J, Kauffmann F. Role of gender and hormone-related events on IgE, atopy, and eosinophils in the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy. *J Allergy Clin Immunol* 2004;114:491-8
32. Le Roux P, de Blic J, Albertini M, Bellon G, Body G, Bremont F, Caurier B, Chomienne F, Counil F, Dalphin L, David V, Delacourt C, Deneuille E, Derelle J, Deschildre A, Donato L, Dubus JC, Fayon M, Garcia J, Heuze L, Houzel A, Just J, Labbe A, Lesbros D, Mahraoui C, Malfroot A, Marguet C, Monrigal P, Pautard JC, **Pin I**, Rayet I, Sardet A, Scalbert M, Siret D, Troadec C. [Flexible bronchoscopy in children. Experience at French centers of pediatric pneumology]. *Rev Mal Respir.* 2004 ;21(6 Pt 1):1098-106.
33. Bouzigon E, Dizier MH, Krahenbuhl C, Lemainque A, Annesi-Maesano I, Betard C, Bousquet J, Charpin D, Gormand F, Guilloud-Bataille M, Just J, Le Moual N, Maccario J, Matran R, Neukirch F, Orszczyn MP, Paty E, **Pin I**, Rosenberg-Bourgin M, Vervloet D, Kauffmann F, Lathrop M, Demenais F. Clustering patterns of LOD scores for asthma-related phenotypes revealed by a genome-wide screen in 295 French EGEA families. *Hum Mol Genet.* 2004 ;13:3103-13.
34. **Pin I**, Pilenko C, Chatain P, Llerena C, Bost M. Environnement et asthme de l'enfant : controverses. *Arch Pediatr.* 2004 Jun;11 Suppl 2:93s-97s.
35. Zmirou D, Gauvin S, **Pin I**, Momas I, Sahraoui F, Just J, Le Moullec Y, Bremont F, Cassadou S, Reungoat P, Albertini M, Lauvergne N, Chiron M, Labbe A; Vesta Investigators. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. *J Epidemiol Community Health.* 2004;58:18-23.
36. Le Roux P, de Blic J, Albertini M, Bellon G, Body G, Bremont F, Caurier B, Chomienne F, Counil F, Dalphin L, David V, Delacourt C, Deneuille E, Derelle J, Deschildre A, Donato L, Dubus JC, Fayon M, Garcia J, Heuze L, Houzel A, Just J, Labbe A, Lesbros D, Mahraoui C, Malfroot A, Marguet C, Monrigal P, Pautard JC, **Pin I**, Rayet I, Sardet A, Scalbert M, Siret D, Troadec C. Fibroscopies bronchiques chez l'enfant. Expérience des centres français. *Rev Mal Respir* 2004 ;21(6 Pt 1):1098-106
37. **Siroux V**, **Pin I**, Pison C, Kauffmann F. Asthme sévère en population générale : définitions et prévalence. *Rev Mal Respir* 2004 ;21:961-969
38. **Siroux V**, Kauffmann F, Pison C, **Pin I**. Caractère multidimensionnel de la sévérité de l'asthme dans l'enquête EGEA *Rev Mal Respir* 2004 ;21:917-924

2005

39. Le Moual N, **Siroux V, Pin I**, Kauffmann F, Kennedy SM; Epidemiological Study on the Genetics and Environment of Asthma. Asthma severity and exposure to occupational asthmogens. *Am J Respir Crit Care Med.* 2005 ;172:440-5.
40. Varraso R, **Siroux V**, Maccario J, **Pin I**, Kauffmann F; Epidemiological Study on the Genetics and Environment of Asthma. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005 ;171:334-9.
41. Dizier MH, Bouzigon E, Guilloud-Bataille M, Bétard C, Bousquet J, Charpin D, Gormand F, Hochez J, Just J, Lemainque A, Le Moual N, Matran R, Neukirch F, Oryszczyn MP, Paty E, **Pin I**, Vervloet D, Kauffmann F, Lathrop M, Demenais F, Annesi-Maesano I. Genome screen in the French EGEA study : detection of linked regions shared or not shared by allergic rhinitis and asthma . *Genes Immun* 2005 ;6:95-102.
42. Graves PE, **Siroux V**, Guerra S, Klimecki WT, Martinez FD. Association of atopy and eczema with polymorphisms in T-cell immunoglobulin domain and mucin domain-IL-2-inducible T-cell kinase gene cluster in chromosome 5 q 33. *J Allergy Clin Immunol* 2005 ;116:650-6.
43. Janson C, de Marco R, Accordini S, Almar E, Bugiani M, Carolei A, Cazzoletti L, Cerveri I, Corsico A, Duran-Tauleria E, Gislason D, Gulsvik A, Jogi R, Marinoni A, Martinez-Moratalla J, **Pin I**, Vermeire P, Jarvis D. Changes in the use of anti-asthmatic medication in an international cohort. *Eur Respir J* 2005 ;26:1047-55.
44. Pepin JL, Delavie N, **Pin I**, Deschaux C, Argod J, Bost M, Levy P. Pulse transit time improves detection of sleep respiratory events and microarousals in children. *Chest.* 2005 Mar;127:722-30.
45. Guenégou A, Leynaert B, **Pin I**, Le Moel G, Zureik M, Neukirch F. Serum carotenoids, vitamins A and E, and 8 year lung function decline in a general population. *Thorax.* 2006 ;61:320-6.
46. Guénégou A, Leynaert B, Bénessiano J, **Pin I**, Demoly P, Neukirch F, Boczkowski J, Aubier M. Association of lung function decline with the heme oxygenase-1 gene promoter polymorphism in a general population. European Community Respiratory Health Survey (ECRHS) France. *J Med Genetics* 2006 (in press)
47. Shaaban R, Kony S, Driss F, Leynaert B, Soussan D, **Pin I**, Neukirch F, Zureik M. Change in C-reactive Protein Levels and FEV1 decline: a longitudinal population-based study. *Respir Med.* 2006; (in press)
48. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, Carolei A, Cazzoletti L, Corsico A, Gislason D, Gulsvik A, Jögi R, Marinoni A, Martínez-Moratalla J, **Pin I**, Janson C. Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006: (in press)

GRANTS

2000

PHRC national: 2000-2002 : n° 2610 2000-2002 : Etude longitudinale sur les facteurs liés à l'incidence des symptômes d'asthme et de l'atopie, et à la diminution de la fonction pulmonaire chez les adultes jeunes ayant participé à European Community Respiratory Health Survey– I (ECRHS-II)

Demandeur : I Pin

Ministère de l'environnement - Programme santé environnement 2000

Contrat Environnement Santé 2000 N° AC013G

Nom du contrat : Etude épidémiologique des facteurs Génétiques et Environnementaux

de l'Asthme, l'hyperréactivité bronchique et l'atopie (EGEA) 1991- 2001

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

Nom du contrat : Facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) - Etude longitudinale sur 10 ans : 1991 - 2002

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

Nom du contrat : Persistance, rémission, aggravation de l'asthme de l'enfant - Etude longitudinale 1992-2005

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

Nom du contrat : Environnement, asthme, allergie : vers une approche vie entière - Etude épidémiologique des facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) 1992-2005

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 ADAM33 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 Autònoma de Barcelona
1979 Specialist in Respiratory Medicine, Universitat Autònoma de Barcelona
1990 PhD, Universitat Autònoma 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

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Born 14 October 1957

Training

1980 MD Univesitat 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 de Barcelona)
1988 Epidemiologist, Dept Epidemiologia y Salud Publica, IMIM
1990 Associate Professor, Salud Publica y Med Preventiva, Universidad 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, Insstitute for Social and preventive medicine
2001-2002 Assistant professor, University of Basel
2002-2005 Associate Professor, Unisersity 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 committes at the interface of science and policy (WHO, EPA, ..)

Themes of research : Exposure to and chronic main health effects of ambient air pollution



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Training

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1998 PhD Environmental and Occupational Health, Wageningen, The Netherlands

Appointments

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Training

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2002 PhD Public Health and Methodology on Biomedical research, Universitat Autònoma de Barcelona

Appointments

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Training

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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)

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PUBLICATIONS 2000-2006 (RESPIRATORY AND SELECTED OTHERS)

2000

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2. **Antó JM, Sunyer J, Kogevinas M**. *Environment and health: the long journey of environmental epidemiology at the turn of the millennium*. J Epidemiol & Biostatistics 2000; 5: 49-60.
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4. **Antó JM**, Vermeire P, **Sunyer J**. *Chronic obstructive pulmonary disease*. En: Annesi-Maesano I, Gulsvik A, Viegi G, eds. Respiratory Epidemiology in Europe. Huddersfield: European Respiratory Society, 2000: 1-22.
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GRANTS

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,
Period: 2003-2007
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 stressors 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
Period: 2004-2007
Import: 24.000 euros
IP: Manolis Kogevinas

Title: Environment, genes and asthma: an international study.
Financing: Fundació La Marató de TV3
Period: 2005-2007
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: Assesment & 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 inflamatory response in myocardial infraction 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