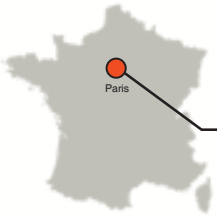
# COBRA:

## COhort, BRonchial obstruction and Asthma

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## OVERVIEW

### AT A GLANCE

> Immuno-inflammation
> Asthma & COPD
> Coordinated by Michel Aubier
> Inserm sponsorship
> Major grants: Legs Poix, Inserm & private companies
> Asthma, biomarkers, therapeutic targets

### KEY FACTS & FIGURES

> Current status: inclusion on-going: 1,200 asthmatic patients & 265 COPD patients already enrolled
> 2,000 asthmatic & 1,000 COPD expected patients
> 10-year follow-up
> Multicentric cohort (14 sites around France)
> Biobank: serum, DNA, induced sputum, bronchoalveolar lavage and bronchial biopsies

COBRA is the first prospective cohort of **asthmatic and COPD** patients in France associated with a biobank (serum and DNA). Its originality relies on the parallel follow-up of 2 cohorts. This cohort will allowed to **evaluate evolution of biomarkers** implicated in severity by proteomic technologies and to determine **genetic risk factors** by a genetic approach.

COBRA focuses on the cellular and molecular mechanisms involved in the pathogenesis of airway and alveolar inflammation and remodeling in severe asthma and COPD.


### Positioning

> COBRA is closely working with the ECRHS, the first study to assess the geographical variation in asthma, allergy and allergic sensitization and PAX-LASER cohort, study of patients with uncontrolled severe asthma in real-life

> COBRA is involved in AirPROM project (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling). AirPROM is an EU-funded project that brings together 34 partners with expertise in physiology, radiology, image analysis, bioengineering, data harmonization, security and ethics, computational modelling, systems biology, and health communication

> Partnership with pharmaceutical companies are already on-going

# LEADERSHIP

***COBRA's leadership team is set up with a tandem of the renown biostatistician, Nicolas Molinari, and clinician, Michel Aubier, who have been committed in the field for 15 years.***

## Dr. Michel AUBIER, Head Pneumology department, Bichat Hospital, Paris

**Director of the Clinical Investigation Center Hospital Bichat, Paris, France**

**Co-leader team 2 Inserm Unit 1152 "Mechanisms of airway inflammation and remodeling in severe asthma and COPD"**

**Awards**

> Environment Health award - French Academy of Medicine
> Shubin Memorial Lecture Award - Society of Critical Care Medicine, New York, USA

**Expertise**

> Expert for the National Clinical Research Program (PHRC) and the National Research Agency (ANR)
> Scientific expert for the former AERES (French research evaluation agency)

**Scientific evaluation & Committee Membership**

> Member of the Inserm « Conseil d'Orientation et de Réflexion Stratégique (CORES)
> Vice-Dean of the Faculty of Medicine Xavier Bichat (University Paris 7)

**Current Collaborations**

> CPC/Helmholtz Center, Munich, Germany
> Centre National de Génotypage, Évry
> Proteomic platform of Institut Jacques Monod, Paris

## Nicolas MOLINARI, Associate Professor of Biostatistics, Montpellier 1 University, Montpellier University Hospital

**Expertise**

> Expert for the National Clinical Research Program (PHRC) and the National Research Agency (ANR)
Scientific expert for ANSM (French FDA)
> Expert for the « Délégation à la Recherche Clinique et à l'Innovation » Montpellier University Hospital

**Committee Membership**

> Member of the «Comité de Protection des Personnes» Sud –Méditerranée III
> Member of the management board of UFR Médecine Montpellier-Nîmes
> Treasurer of the "Société Française de la Statistique" (Biopharmacie-Santé)

**Student supervising**

> Ph.D.: 11
> Master: 32

**107 scientific publications (statistic and medicine)**

# SCIENTIFIC NETWORK & MANAGEMENT

**Michel Aubier's Investigation Center was involved in following studies:**

> The **ECRHS**, the first study to assess the geographical variation in asthma, allergy, and allergic sensitization in adults using the same instruments and definitions, the European Community Respiratory Health Survey (ECRHS). This study approximately enrolled 140,000 individuals aged 20-44 years from 22 countries.
> The **EuroSMART** study, by Michel Aubier, evaluated the potential benefit of increasing the maintenance dose of budesonide/formoterol maintenance and reliever therapy. The study was a 6-month, randomised, open-label, pan-European investigation involving 8,424 adult asthmatic patients.
> The **SITAX** study, by Michel Aubier, evaluated the effect of a Receptor Antagonist of Endothelin 1 (Sitaxsentan, Thelin) on Bronchial Remodeling in Severe Asthma With Fixed Bronchial Obstruction. Changes in airway remodeling was analyzed on bronchial biopsy specimens at inclusion and after one year by immunohistochemistry and morphometry (smooth muscle area, and submucosal fibroblasts count)
> The **AirPROM** project is an EU-funded project that brings together 34 partners with expertise in physiology, radiology, image analysis, bioengineering, data harmonization, security and ethics, computational modelling, systems biology, and health communication.
**Chitinase study** in asthma and COPD: Expression and role of chitinases in asthma and COPD

**Through its Scientific Committe, COBRA involves experts in:**

> **Clinical management of asthmatic and COPD patients:** Michel Aubier, Marc Humbert, Bruno Housset, Daniel Dusser, Gérard Huchon, Thomas Similowski, Bernard Maitre, Pascal Chanez, Jean François Bervar, Philippe Godard, Patrick Berger, Antoine Magnan, Anne Prudhomme, Charles Hugo Marquette, Frédéric de Blay
> **Expert in inflammation, eosinophil, asthma, bronchoalveolar lavage, and eosinophil apoptosis:** Marina Pretolani
> **Biobanking:** Joelle Benessiano
> **Biostatistics:** Nicolas Molinari

# PROJECT DESCRIPTION

## SCIENTIFIC OBJECTIVES

- The aim of this national, multicenter, prospective, clinico-biological study of 2 cohorts of asthmatic and COPD patients is to evaluate evolution of biomarkers implicated in severity by proteomic technologies and to determine genetic risk factors by a genetic approach
- Control of short term events, exacerbations and overall severity are markers of management efficiency. In this field, longitudinal data are urgently required in order to improve a better phenotyping, an important profiling work dedicated to personalized cares
- In severe asthma patients, Cobra will allowed to identify clear biomarkers, better understanding in the physiopathology including genetic and epigenetics associated factors, and an assessment of the future risk for patients
- At a glance, constituting biological sample bank in chronic airway diseases is the unique opportunity to improve management, understanding, predict exacerbation and institute early interventions based on biomarker identification and potential genetic susceptibilities

## INNOVATIVE SCIENTIFIC FEATURES

- 5-year first follow-up phase with visit every 6 months and a second 5 year follow-up phase with visit every year
- Originality in cohort constitution
- Data of quality collection

## METHODOLOGY QUALITY

- Data monitoring : completeness of patient records, accuracy of entries on the CRFs, adherence to the protocol and to Good Clinical Practice (GCP)
- Good Clinical Practice Quality Assurance performed by a dedicated Inserm unit

# DESIGN, METHODOLOGY & TIMELINE


| | |
|---|---|
| **Recruitment objectives:** | 2,000 asthmatic and 1,000 COPD enrolled patients. |
| **Sites:** | 14 clinics centers widespread in France |
| **Inclusion criteria:** | *Athsma:* Men & women; 18-80 years; smoker or non smoker asthmatic patient; with or without reversibility on PFT (pulmonary Function Tests) with well documented diagnostic of asthma<br>*COPD:* Men & women; 18-80 years; current or past smoker (>10 pack-years) with symptomatology of COPD with or without bronchial air obstruction (FEV/FVC ≤70%) with improvement of FEV less than 10% after inhalation of 400 µg of salbutamol |
| **Exclusion criteria:** | Refusal the patient to participate to the follow-up (10 years) or to the constitution of the biological collection |

**INCLUSION COLLECTION**
**Database:** the collected data range from socio-demographic, environmental, and bio-clinical data, treatments, and health care provider.
**Biobank:** serum, DNA, & PBMC

**FOLLOW-UP: VISIT EVERY 6 MONTHS (0 TO 5 YEARS) AND EVERY 12 MONTHS (5 TO 10 YEARS)**
**Database:** in addition to socio-demographic, environmental, and bio-clinical data, concomitant treatment, and health care provider recording, follow-up database record adverse event and serious adverse event

**Biobank:** serum, PBMC, BAL, bronchial biopsy, induced sputum

# DATABASE & BIOBANK CONTENTS

## DATABASE

**Demographic:** initials, date of birth, sex, geographic origin, professional activity

**Risk factors:** smoking

**Clinic:** relevant personal and familial medical history (Asthma cohort: eczema, asthma, rhinoconjunctivitis; COPD cohort: asthma, chronic bronchitis, emphysema, respiratory insufficiency), complete physical examination

**Biologic:** skin prick test was performed for the most common pneumallergens, pulmonary function tests, 6-minute walk test (COPD cohort), blood gas (COPD cohort), pulmonary high blood pressure evaluation (COPD cohort), CT-scan (COPD cohort if not performed within 12 months) bronchial hyper responsiveness test (COPD cohort), bronchial fibroscopy (COPD cohort)

**Therapeutic:** concomitant medication

**Imaging:** CT scan for all patient with COPD at inclusion

**Quality of life:** patient is to be questioned regarding quality of life with a validated Juniper questionnaire (Asthma cohort)

## BIOBANK

**Originality**

> Large number of patients with longitudinal follow-up with serial biological samplings

**Scientific objective**

> Biobank aims to carry out future studies on:
>> Biomarker identification notably through -omic technologies
>> Cell signaling (cytokines, chemokines) in chronic bronchic inflammation
>> Airway remodeling
>> Pathogenic mechanisms

> Biobank is already associated with several projects:
>> Role of PAR-2/ligands overexpression and airway smooth muscle in severe asthma
>> Bronchial thermoplasty and severe asthma

**Samples**

> Asthma cohort: eosinophils, total IgE, specific IgE
> COPD cohort: α1-antitrypsin, α1-antitrypsin genotype if required, erythrocytes, lymphocytes, eosinophils, monocytes, High sensitivity CRP.
> 14 aliquots (250µl) per patient for serum
>> 1,465 patients with DNA and serum sampling

> 4 biopsies per patient who underwent bronchoscopy
>> 350 asthmatics with bronchial biopsies and BAL
>> 90 COPD with bronchial biopsies and BAL

> Total number of samples: 60,000

**Associated resources**

> COBRA cohort has 2 technicians dedicated to sample management

# TECHNICAL MODALITIES & SPECIFICATIONS

## ORGANIZATION

- Biological samples collection, treatment, and **storage** is organized and **performed by Bichat Biological Resources center**
- Each biological sample is identified by a patient-specific code. The clinical database hosts each patient-specific code for traceability

## SPECIFICATIONS

- All asthmatic patients and COPD patients included in COBRA cohort are eligible for sampling
- Date of the first sampling: 01/07/2008
- **Sampling frequency:**
  - > At baseline and each follow-up visit for serum sampling
  - > At baseline for DNA
  - > When possible during baseline or follow-up for PBMC
  - > In patients in whom invasive procedures are required, bronchoscopy allows to sample the Bronchoalveolar lavage (BAL) and bronchial biopsies.
- Responsible for the biobank: Nathalie Seta
- Protocol for the biological sample collection exists and is available on demand
- **100 clinical items are associated with each sample**
- **Label of quality:** samples are transferred from each site to the BRC Bichat Hospital for DNA extraction and serum collection. All samples are stored to BRC Bichat hospital at -80°C in a secure environment according to internal BRC procedures. This BRC is a certified organization with standard NF S95-900 (Ref. 2009/34457).
- Biobank procedures has been developed in order to **apply standardized methods for sample collection, treatment and conservation** (Standard Operating Procedure)
- COBRA biological samples are **available by now**

# BIOLOGICAL SAMPLE COLLECTION & ACCESS

| Biological specimens | Origin | Quantity / concentration available | No. of aliquots | No. of subjects who have been/will be sampled (ongoing/ expected) | Storage conditions |
|---|---|---|---|---|---|
| At Baseline (date of the first sampling): 7th July 2013 | | | | | |
| **Serum** | Blood | 250 µg | 14 | 1,200/2,000 | -80°C |
| **DNA** | Blood | 300 µg | 10 | 1,200/2,000 | -80°C |
| **PBMC** | Blood | 7 tubes with 7 mL | | | |
| During the follow-up : every 6 months (from baseline visit to 5 years follow-up) and every 12 months (from 5 to 10 years follow-up) | | | | | |
| **Serum** | Blood | 250 µg | 14 | 1,200/2,000 | -80°C |
| **PBMC** | Blood | 7 tubes with 7 mL | | | |
| **BAL** | Bronchoscopy | | variable | 250 | |
| **Bronchial biopsy** | Bronchoscopy | | 2 | 350 | Paraffin-embedded |
| **Bronchial biopsy** | Bronchoscopy | | 2 | 350 | Frozen |
| **Induced sputum** | | | variable | 250 | |

## BIOBANK SAMPLE ACCESS MODALITIES

- A document specifying biobank access is available since 2008
- Serum & DNA samples are accessible to public as well as to industrial research teams; bronchial biopsies and broncho-alveolar lavage are accessible under specific conditions
- Specific biological samples access will be granted on the acceptation of the research protocol submitted to the scientific committee
- Biological sample transfer is allowed if approved by the scientific committee
- Biological samples are also shareable with a foreign company

## BIOLOGICAL SAMPLE ANALYSES

- The COBRA cohort envisages to exploit the biological samples to:
  - > Biomarker and -omic studies
  - > Cell signaling (cytokines, chemokines) studies in chronic bronchic inflammation
  - > Airway remodeling studies
  - > Responses studies to identify pathogenic mechanisms
- To date, there is no biological sample analysis-derived data. When available, access request to these data should be submitted to the scientific committee

# RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

## Translational research

> Discover biomarkers to better predict the prognosis and response to treatments

> HMGB1 is augmented in COPD and is associated with IL-1beta and RAGE

> Study of chitinase with chitinolytic activity selectively augmented in COPD and its contribution to pathogenesis

> Expression and function of IL-33-ST2 interaction in severe asthma: genetic and biological studies

> New therapeutic targets for severe asthma

> Identification of novel immuno-inflammatory phenotypes or airway inflammation

## Clinical development

> Molecular phenotyping of steroid refractory asthma

> Develop new personalized treatment targets/strategies adapted to a given phenotype such as endothelin-1 receptor antagonist

> Understand the patho-immunobiology of the different severe asthma phenotypes

## Outcomes research

> Real-life treatment of asthma exacerbations

> Difference between asthmatic smokers and non-smokers on maintenance and reliever therapy

> Pharmaco-economic studies cost/benefit; Health economic outcomes.

> Comparative studies to assess respiratory product efficiency

> Quality of life studies

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