COHORT INNOVATION DAY

Academic book

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INTRODUCTION

Aviesan (Alliance for Life Sciences and Health) and ARIIS (Alliance for Research and Innovation in Health Industries) have jointly set-up this Cohort Innovation Day (CID - March 21, 2014), with the spirit of fostering and promoting public/private collaborations around existing high potential epidemiological and translational research platforms.

France has a long tradition and excellent track-record in the field of epidemiology and research in public health, associated to world-class capabilities in clinical research. In the recent years, a number of initiatives have led to a further strengthening and development of national research infrastructures, often in connection with similar European networks. These infrastructures include a number of important and innovative cohorts and research platforms in various therapeutic domains.

In the program of the Cohort Innovation Day, 16 cohorts have been rigorously selected based on a number of criteria, including scientific excellence, competitive positioning, unique differentiating features, extent and quality of the database, associated features (i.e., biobanks using state-of-the-art methodology, imaging data, etc…), scientific leadership and track-record of the cohort leadership team.

It is expected that all these cohorts have a strong potential for some form of public-private partnership with industrial partners. Potential collaborations can be of various types, and can encompass all aspects of the value chain :

> from early research (physiopathology, study of clinical and biological correlates, pharmacogenomics, generation of new hypotheses, development or validation of biomarkers, disease-models, translational research etc…)

> to clinical development (implementation of sub-studies, or nested trials, patients segmentation, identification of target population, development and validation of study endpoints, access to well-characterized and annotated biological samples and/or imaging data, etc..)

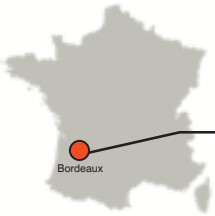
> and « real-life » studies (pharmaco-epidemiological studies, socio-economic studies, QoL studies, benefit/risk assessment, long-term follow-up, etc…).

Cohorts on the program include disease-specific cohorts in several important therapeutic areas, as well as general population cohorts, pediatric cohorts, and cohorts in rare diseases.

By combining the scientific strength of academic research teams involved in the design and set-up of these cohorts and associated research and biobanks platforms, with the skills, outcome orientation and capabilities of Health Industry partners, we wish to progress towards addressing important scientific and industrial challenges.

***Pr. Jean-Paul Moatti*, Director, Aviesan Institute for Public Health**

BCB-SARCOMES



Pr. Jean-Michel COINDRE
PU-PH, University Bordeaux, INSERM U916, Pathology Institut Bergonié

Pr. Simone MATHOULIN-PELISSIER
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OVERVIEW

AT A GLANCE

> Oncology
> Sarcomas Patients, including Gastro Intestinal Stromal Tumuor (GIST) and desmoid tumors
> Coordinated by Pr. Coindre and Pr. Mathoulin-Pelissier
> University Bordeaux Sponsorship
> Funded by INCa

KEY FACTS & FIGURES

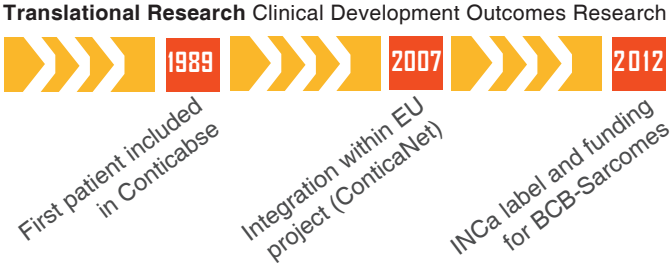
> Status: Inclusion ongoing
> Integration and inter-operability of 3 major existing databases in the field:
>> Conticabase, 13 600 patients
>> RRePS, 17 000 patients
>> NetSarc, 19 000 patients
> 90% of approximately 4-5000 new cases per year in France will be part of BCB-Sarcomes Recruitment through French Sarcoma Group (in existence for > 15 years)
> Extensive annotated Biobank
> Linkage with FRANCIM registry

BCB-Sarcomes is designed as a nation-wide comprehensive multidisciplinary epidemiological, clinical, biobank, pathological and translational research platform.

The major objectives are:
>> Better understanding of biology in order to improve diagnosis and prognosis and set-up new treatments
>> Improvement of medical practices and patient's management
>> Evaluation of potential environmental and socio-economic factors in the development of these tumors

Sarcomas include a large variety of rare mesenchymal cancers, whose incidence and biology is still poorly undestood.

Part of BCB-Sarcomes, the Conticabase contains data on 13 000 patients with annotated frozen tissue for 7000 tumors. It represents an important resource for research on these important cancers.



Positioning

> Given sarcoma rarity as a group, but even more as individual entities, research and clinical trials in specific histological and molecular subtypes of sarcoma can only be performed through integrated clinical networks, centres of clinical excellence, supported by translational research.
> BCB Sarcomes provides for an integrated platform of three key databases fed by reference national networks of investigators, associated to a comprehensive state-of-the-art Biobank.
> The project is well connected with EU FP-7 initiatives such as ConticaNet and EUROSARC.
> Link with FRANCIM Cancer registries.
> Successful track-record of collaboration with industry..

LEADERSHIP

Pr. Jean-Michel Coindre
University of Bordeaux, INSERM U916
Pathology, Institut Bergonié, Bordeaux

- Coordinator of the national network for histological review of sarcomas, GIST and desmoid
- Coordinator of the national post-graduate teaching on soft tissue tumors
- Current collaborations with:
  - >> University Hospitals Leuven
  - >> M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology (Warsaw)
  - >> University Hospital Muenster (Germany)
  - >> University of Treviso (Italy)
  - >> Memorial Sloan Kettering Cancer Center (New York)
  - >> Brigham and Women Hospital (Boston)

Pr. Simone Mathoulin-Pelissier
INSERM CIC 1401/Université Bordeaux, ISPED
and Clinical Research Unit Bergonié

- Extensive experience in the cohort field (population or hospitals) and clinical research studies (clinical trials, diagnosis and prognosis studies)
- Coordinator of CIC 1401, Cancer Axis, Bordeaux (Inserm) and Clinical Trial Unit (INCa)
- Co-coordinator of National BCB Hepatocarcinoma (INCa)
- Coordinator of National Oncogeriatric PF (Ligue nationale cancer)
- Current collaborations with:
  - >> Environment and occupational unit (Bordeaux Inserm)
  - >> EORTC statitistics (Bruxelles)
  - >> NCI, trial unit (USA)
  - >> Fes University, Public health and epidemiology (Morocco)

SCIENTIFIC NETWORK & MANAGEMENT

- The Institut Bergonié Sarcoma Group is a multidisciplinary team with proven track-record in this field, coordinating the national sarcoma pathology group since 1989 and involved in numerous large International projects (FP6 ConticaNet, FP7 Eurosarc)
- The Institut Bergonié Sarcoma Group has been a co-founder with Centre Léon Bérard (Pr. Jean-Yves BLAY, Lyon) and Institut Gustave Roussy (Villejuif) of the French Sarcoma Group
- BCB-Sarcomes involves the three French national networks dedicated to sarcoma (NetSarc - 40 centres and 300 researchers/clinicians, and RRePS - 22 pathology centres as well as ResOs) representing 90% of all sarcoma patients in France
- As part of the EU ConticaNet Network of Excellence, BCB-Sarcomes is responsible for establishment of the virtual annotated tumor banks on mesenchymal tumors (ConticaBase and ConticaGist). These databases contain about 15 000 patients with >7000 frozen and highly annotated tumor fragments
- A Scientific Committee is the supervising body in charge of approving research projects willing to exploit the BCB Sarcomes Database. Its composition is as follows:

>> RJY. Blay (Lyon)
>> A. Lecesne (Villejuif)
>> F. Gouin (Nantes)
>> G. de Pinieux (Tours)
>> Ph. Rosset (Tours)
>> BN. Bui (Bordeaux)
>> JO. Bay (Clermont-Ferrand)
>> B. Tomeno (Paris)
>> F. Chibon (Bordeaux)
>> N. Penel (Lille)
>> S. Bonvalot (Villejuif)
>> Ph. Anract (Paris)
>> M. Delannes (Toulouse)
>> E. Mascard (Paris)
>> S. Taïeb (Lille)
>> F. Duffaud (Marseille)
>> C. Chevreau (Toulouse)
>> O. Collard (Saint-Etienne)
>> F. Goldwasser (Paris)
>> A. Italiano (Bordeaux)
>> P. Marec-Bérard (Lyon)
>> D. Orbach (Paris)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

BCB-Sarcomes is designed as a nation-wide comprehensive data-warehouse platform including extensive epidemiological, clinical and biological data concerning sarcomas, based on a number of existing databases

The goal is to provide researchers with an integrated and high-quality research platforms aiming at:

> Better understanding of biology in order to improve diagnosis and prognosis and set-up new treatments

> Improvement of medical practices and patient's management

> Evaluation of potential environmental and socio-economic factors in the development of these tumors

INNOVATIVE SCIENTIFIC FEATURES

> Unique in its scope and ambition (number of patients, extent of data collection, quality of biological samples)

> Carefully annotated bio-banking of frozen tissues

> Extensive national recruitment through existing national networks

> Linkage with French Cancer Registry (FRANCIM)

> Unlimited follow-up

> Use of I2B2 and TransMart with integration of "omics" data

METHODOLOGY QUALITY

> Secure web-access database

> Professional data-management provided through CIC, with thorough QA process

> Systematic secondary pathology review

> EU integration within Conticanet

> Label INCa and CNIL authorization

> Defined model of data

> Follows international standards (LOINC, UMLS)

> NFS 96-900 certification of the network is underway

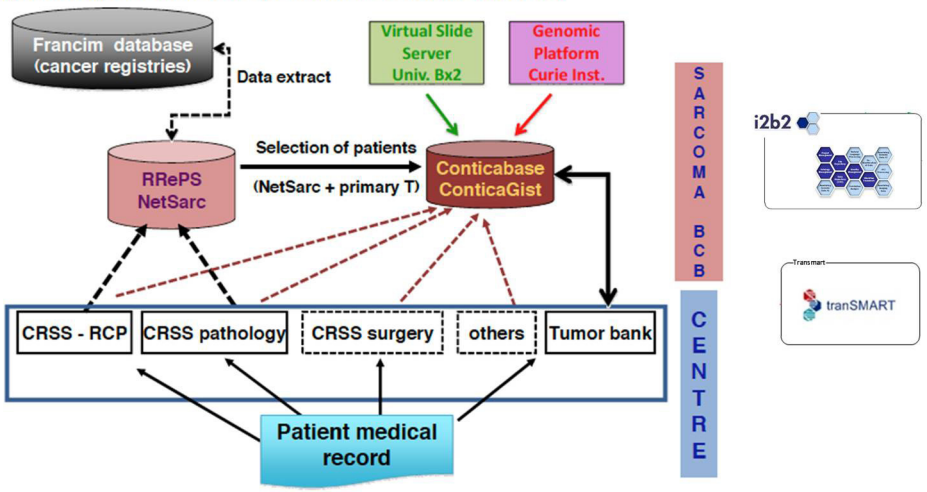
DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	The recruitment in Conticabase and NetSarc is about 2000 new patients per year. There are about 4 000 new patients per year in RRePS
Sites:	Netsarc, the national reference network for sarcomas coordinates 24 regional sarcoma tumor board (referal centres) The network of Reference for Sarcoma Patholgy (RRePS) consist of 22 centres
Inclusion criteria:	Every new case of sarcoma, GIST, desmoid tumor
Exclusion criteria:	Lack of informed consent

INCLUSION COLLECTION
Database: Conticabase contains 170 parameters on demographic, clinical, histological, pathological and biological description, and treatments received
Biobank: Tumor and normal tissue. Frozen samples and paraffin-embedded; RRePS contains 31 detailed parameters on secondary pathology review

FOLLOW-UP: UNLIMITED
Database: Clinical follow-up, medical events, therapeutic management
Biobank: Follow-up on biosamples

Figure 1. BCB sarcoma structure and links with other databases



DATABASE & BIOBANK CONTENTS

Database

> The CONTICABASE database and tumour bank: This database contains information describing the tumour, treatment and follow-up as well as tumour sample availability and molecular biology analyses for mesenchymal tumours except GIST and bone tumours. The content as of February 2014 is as follows:

>> 13 680 Patients

>> 17 604 Samples

More details at: https://conticabase.sarcomabcb.org

> The CONTICAGIST database and tumour bank contains information describing the tumour, treatment and follow-up as well as tumour sample availability and molecular biology analyses for GIST patients:

>> 1 842 Patients

>> 2 282 Samples

More details at: https://conticagist.sarcomabcb.org

> RRePS/ResOs/NetSarc currently contains data on:

>> 17 442 patients in RRePS with 19 559 samples

>> 20 021 patients in NetSarc

>> 996 patients in ResOs (bone sarcomas) with 1 185 samples

More details at: https://rreps.sarcomabcb.org/home.htm & https://netsarc.sarcomabcb.org/home.htm

> ATG-Sarc contains array-CGH and expression profile data from 840 sarcomas, GIST or desmoid tumors

More details at: http://atg-sarc.sarcomabcb.org

> The collection contains frozen and paraffin-embedded tumours and normal tissues, tissue micro-array blocks, derived products (DNA, RNA and proteins), and derived cell lines from tumours in the database

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>> Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait and see policy according to tumor presentation. Salas S, Dufresne A, Bui BN et al. J Clin Oncol 2011;29; 3553-3558

>> Mitotic checkpoints and chromosome instability are strong predictors of clinical outcomes in Gastrointestinal stromal tumours. Lagarde P, Pérot G, Kauffmann A et al. Clin Cancer Res 2012;18:826-838

>> Advanced soft-tissue sarcoma in elderly patients: patterns of care and survival. Garbay D, Maki RG, Blay JY et al. Ann Oncol. 2013;24:1924-30.

>> Genetic profiling identifies two classes of soft-tissue leiomyosarcomas with distinct clinical characteristics. Italiano A, Lagarde P, Brulard C et al, Clin Cancer Res. 2013; 1;19:1190-6.

>> Chromosome instability accounts for reverse metastatic outcomes of pediatric and adult synovial sarcomas. Lagarde P, Przybyl J, Brulard C et al, J Clin Oncol. 2013;31:608-15.

>> Adherence to consensus-based diagnosis and treatment guidelines in adult soft-tissue sarcoma patients: a French prospective population-based study. Mathoulin-Pélissier S, Chevreau C, Bellera C et al. Ann Oncol. 2014 ;25:225-31

>> Retroperitoneal sarcomas: patterns of care in advanced stages, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group. Toulmonde M, Bonvalot S, Ray-Coquard I et al on behalf of the French Sarcoma Group. Ann Oncol 2014;Feb 3. [Epub ahead of print

RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Gene expression signature** related to genome complexity to validated prediction of clinical outcomes in sarcomas

> Develop molecular CINSARC (Complexity INDEX in SARComas) signature as a predictor of the metastatic potential of sarcomas and GIST

> **Identification of potential therapeutic targets** (ATG Sarc and cell lines)

> Chromosome instability in reverse metastatic outcomes

Clinical development

> **Prognostic factors** influencing sporadic desmoid tumors progression

> Predictors of **clinical outcomes** in Gastrointestinal stromal tumours

> Optimization of clinical studies (timing, measures and scales, sub-population characterization, design...)

> Support clinical enrollment

> Epidemiological studies to support market access

Outcomes research

> Diagnosis and treatment **guidelines** in adult soft-tissue sarcoma patients

> **Patterns of care definition in advanced stages of retroperitoneal sarcomas and** advanced soft-tissue sarcoma in elderly patients

> **Epidemiological and pharmaco-epidemiologic studies:** practices patterns, effectiveness, acceptance, drug safety, 'real-world' use, risk/benefit, risk management

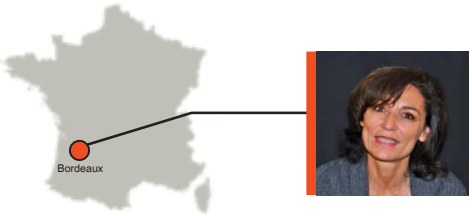
CIADIS :

Chronic Immune Activation - Differentiation - ImmunoSenescence

ANRS CO3 AQUITAINE COHORT

aviesan
ITMO Santé publique

GECSA
Cohorte ANRS CO3 Aquitaine



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OVERVIEW

AT A GLANCE

> Immunology
> Inflammation & aging
> HIV infected patients
> Coordinated by Isabelle Pellegrin & François Dabis
> Bordeaux University Hospital Sponsorship
> Funded by ANRS (Aquitaine Cohort) and pharmaceutical companies (CIADIS project)

KEY FACTS & FIGURES

> CIADIS Status: Inclusion closed, follow-up ongoing
> 1 400 enrolled patients for CIADIS
> Local multi-sites cohort based in Bordeaux University Hospital
> Fresh blood collected at baseline (routine clinic visit in 2012) for assessment of immunological markers
> Serum & DNA Biobanks

Ciadis projects aims to study the impact of chronic Immune Activation (IA), inflammation and immunosenescence (IS) on HIV-related co-morbidities in a large and unselected group of patients within the ANRS Co3 Aquitaine Cohort.

A hallmark of HIV infection is a state of chronic immune activation only partially restored under combination Antiretroviral Therapy (cART). This IA may result in IS and lead to non-AIDS related co-morbidities. We describe here the current status of immunological markers of IA and IS and their association with metabolic disorders, atherosclerosis, kidney disease, neuro-cognitive decline, HCV co-infection, HBV co-infection and cancer events recorded during follow-up in participating patients included in the ANRS CO3 Aquitaine Cohort.

Translational Research Clinical Development Outcomes Research

Positioning

> Ciadis is embedded in the ANRS CO3 Aquitaine Cohort that is part of several HIV European (EuroCoord / Cascade, COHERE and EuroSida) and international networks (ART-CC, D:A:D).

> Aquitaine / Ciadis is also collaborating with the nation-wide French cohort of HIV-HCV co-infected patents (ANRS C013 Hepavih).

> To ensure project sustainability and expansion, Ciadis will be looking for new collaborations.

LEADERSHIP

CIADIS's leadership team is a tandem of renown epidemiologist, François Dabis, and viro-immunologist, Isabelle Pellegrin, who have been committed in this field for 20 years.

Isabelle Pellegrin, Immunovirology, MD, Ph.D. at Bordeaux University Hospital (Pellegrin Hospital, Virology Laboratory during 13 years then Immunology Laboratory since 2008)

- Participation in observational cohorts and cross-sectional studies sponsored by the French National Agency for Research on AIDS and viral Hepatitis (ANRS) via the research team at INSERM Unit 897 on "HIV infections and associated morbidity"
- Coordination of physiopathological, virological, pharmacokinetics and immunological projects in the field of Human Immunodeficiency Virus (HIV) or hepatitis virus infections
- Member of the ANRS work groups "Senescence and comorbidity", "biotheque"
- Member of the ANRS Comité Scientifique Sectoriel 3 "Recherches cliniques et physiopathologiques sur le VIH"
- 15 years experience as member of Independent committees of ANRS (clinical trials)

François Dabis, MD, Ph.D., professor of epidemiology at Bordeaux School of Public Health (ISPED), Bordeaux University, Head of INSERM U897 team "HIV , Cancer & Global Health"

- Founder and Principal investigator (PI) of the Aquitaine Cohort since 1987 (labeled by ANRS as ANRS CO3 in 1992)
- Co-PI of ANRS CO-13 HEPAVIH French-wide cohort of HIV-HCV co-infected patients since its inception in 2006
- PI of International epidemiological Database to Evaluate AIDS (IeDEA) Cohort Collaboration in West Africa (NIH 5-year grant)
- Chair of the ANRS Coordinated Action on research in lower-income countries (AC12)
- Chair of the Scientific Board of the Institut National de la Veille Sanitaire (French Centers for Disease Control) from 2003 to 2012
- Current collaborations: Hepatitis Working Group leader within EuroCoord / COHERE HIV cohort European network, member of Steering Committee of ART-CC Collaboration, D:A:D Collaboration and IeDEA global cohort network

SCIENTIFIC NETWORK & MANAGEMENT

ANRS CO3 Aquitaine Cohort (including CIADIS) is implicated in numerous European Projects:

>> COHERE (Collaboration of Observational HIV Epidemiological Research in Europe): collaborative group of 37 adults, paediatric, and mother/child HIV cohorts across Europe. ISPED/Inserm U897 is one of the two Regional Coordinating Centres

>> CASCADE: Concerted Action on SeroConversion to AIDS and Death in Europe

>> ART-CC: Antiretroviral Therapy Cohort Collaboration

>> D:A:D: Data Collection on Adverse events of Anti-HIV Drugs

ANRS CO3 Aquitaine Cohort (including CIADIS) is also collaborating with French cohorts within the Coordinated Action (AC) n°7 of ANRS:

>> ANRS CO13 HEPAVIH: HIV/HCV co-infected patients

>> ANRS AC11 Resistance Group: HIV-1 genotypic Drug resistance interpretation's algorithms

>> ANRS CO21 CODEX : Cohort of HIV patient with extrem profil: CO15 (Long term non progressors) and CO18 (HIV Controllers)

>> ANRS CO20-CUPIC - NCT01514890: multicentre cohort of the French Early Access HCV Treatment Program

ANRS CO3 Aquitaine Cohort (including CIADIS) can potentially collaborate with relevant ANRS clinical trials (non-inclusive list):

>> ANRS 139 TRIO Trial Group: Phase II study; Long-Term Efficacy and Safety of Raltegravir, Etravirine, and Darunavir/Ritonavir in Treatment-Experienced Patients

>> ANRS 140 Dr.EAM: switch to monotherapy versus tritherapy in HIV patients with viral suppression on HAART

>> TECOVIR: Antihepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV infected patients

>> ANRS-HC27 BOCEPr.EVIH: BocePrevir+peg-IFN+ RBV in HCV/HIV-co-infected Patients with Previous Failure to peg-IFN+RBV

>> ANRS-H26 TELAPREVIH: BocePrevir+peg-IFN+ RBV in HCV/HIV-co-infected Patients with Previous Failure to peg-IFN+RBV.

>> ANRS HB01 EMVIPEG: Efficacy and Tolerance of Peg-interferon Alpha 2a Added to Tenofovir and Emtricitabine in AgHBe Positive HBV-HIV Co-infected Patients

>> GENUPI: Predictive Factors of the Treatment Failure in Hepatitis C Virus

>> ANRS HB02 VAC-ADN: Efficacy and Tolerance of Naked DNA Vaccine in Patients With Chronic B Hepatitis

Aquitaine Cohort / CIADIS Scientific Committee members are well-known researchers in their field:

>> HIV medicine, internal medicine and infectious diseases: Pr. F. Bonnet, M. Dupon, D. Malvy, P. Mercié, P. Morlat, D. Neau and JL. Pellegrin, Dr. V. Gaborieau, D. Lacoste and S. Tchamgoué (Pr. P. Morlat was the Chair of the 2013 Natonal Guidelines Committee for HIV Medicine)

>> Virology : Pr. H. Fleury

>> Clinical pharmacology: Pr. D. Breilh; Dr. S. Bouchet

>> Epidemiology and Biostatistics: Pr.s G. Chêne, F. Dabis and R. Thiébaut, Dr. L. Wittkop

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

The aim of the CIADIS cohort, nested within the ANRS C03 Aquitaine Cohort, is to measure the **inflammation and aging process**, i.e., the Chronic Immune Activation (CIA), inflammation and immunosenescence (IS) according to:

> Demographic and epidemiologcal variables: age, se, HIV infection duration
> Duration of viral suppression on cART
> Immunological status (CD4+ nadir, duration of CD4+ count level above 500/mm^3 in the absence of treatment; proportion of patients with stable CD4+count >350 mm^3 or >500/mm^3 on cART)
> Antiretroviral regimens and their duration

And to correlate these conditions with cumulative incidence (retrospective), prevalence (cross-sectional) and incidence rate (prospective) of co-morbidities (with validation of each morbid event through a dedicated investigation):

> **Osteoporosis** ("TISSOS" study) (Cazanave et al. AIDS 2008)
> **Cardiovascular** (SUPRA" study) (Badiou S et al. J Infect 2008)
> **Kidney disorders** ("TAHIVA" study) (P. Morlat et al. PLOS One 2013; FA. Dauchy et al. Kidney Int 2011)
> **HIV/HCV co-infection** (Lawson-Ayayi, S et al. JAIDS 2013)
> **Cancer** (Bruyand M et al. J Hepatol 2011; Bruyand M et al. J Clin Virol 2011; Bruyand M et al. Clin nfect Dis 2009)

INNOVATIVE SCIENTIFIC FEATURES

> ANRS C03 Aquitaine Cohort is a 25 years old platform for HIV clinical research including natural history data
> Systematic enrolment in public hospitals on a geographical base (southwestern France) allows representativeness and distribution of patients of both genders and all HIV transmission categories
> Quality checks are based on regular independent audits according to the international standard of the D:A:D Collaboration

METHODOLOGY QUALITY

> Data collection forms have been regularly updated over time to adapt to research needs and clinical practice in HIV medicine
> e-CRF has now replaced paper-based record forms
> Biobank has been set up in 2006 and a collection of 44 000 aliquots (2 000 patients) is centrally stored

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:

ANRS CO3 Aquitaine Cohort: Enrolment still ongoing (3 800 patients included 1987-2013)
1 400 have been enrolled in **CIADIS study**

Sites:

ANRS CO3 Aquitaine Cohort Sites: Bordeaux University Hospital clinic wards and eight public hospitals located in the Aquitaine region, South Western, France

Inclusion criteria:

> Patients included in the ANRS C03 Aquitaine Cohort and currently followed irrespective to CD4+ cell count level, HIV-1 RNA load, HBV or HCV infection status, ART naïve or experienced

> ANRS CO3 Aquitaine Cohort Inclusion criteria: HIV-1 infection confirmed by a Western-Blot test, age over 12 years, in-or outpatient of the participating hospital units; Informed consent given

> The CIADIS cohort is constituted by the patients included, with longitudinal data available. For all cohort patients alive and followed, a specific consent is required for participating to the biological bank, implemented since 2006

ANRS CO3 AQUITAINE COHORT

Database: A standardized e-CRF with epidemiological, clinical, biological and therapeutic data is completed by physicians and research nurses at each clinic contact

Biobank (since 2006): Serotheque and a cellulotheque with an annual sampling for naive or on ART patients and a sampling at the time of the prescription of the first antiretroviral therapy

CIADIS

Database: In addition to Aquitaine Cohort e-CRF, CIADIS collects Immunological markers and Comorbidities parameters

Biobank: The day of the annual sampling intended for the biotheque, without additional blood sample, the fresh blood needed for the measure of routine immunological marker will be used for CIADIS measurements

DATABASE & BIOBANK CONTENTS

Database

> **Datas collected between January 1st, 1987 and today within the ANRS CO3 Aquitaine Cohort, under routine clinical management are available for the CIADIS. These data include:**

>> **Epidemiological factors** (age, gender and HIV transmission category) and **antecedents**

>> **Laboratory measurements** (HIV RNA, CD4 and CD8 cell count, CD4 nadir, biochemical and haematological markers, hepatitis B and C, CMV, EBV serological and PCR status)

>> **Therapeutic interventions** (infectious prophylaxes, statin, cardio-vascular and osteoporosis preventive treatment…)

> **Comorbidities are currently intensively studied in different subgroups of the ANRS CO3 Aquitaine cohort, which provide data from DEXA, IRM, Fibroscan, neurocognitive and locomotor testing for CIADIS**

> **In addition, CIADIS collects**

>> **Immunological markers:**

> CIA markers on CD3+CD4+ and CD3+CD8+ lymphocytes: CD38, HLA-DR and CD38/HLA-DR coexpression

> Differentiation/maturation markers on CD3+CD4+ and CD3+CD8+ lymphocytes: naive LT (TN): CD45RA+CD27+ ; effector memory (TEM): CD45RA-CD27-, effector memory terminally differentiated (TEMRA): CD45RA+CD27-, central memory (TCM): CD45RA-CD27+)

> Immunosenescence markers on CD3+CD4+ and CD3+CD8+ lymphocytes: CD28-CD57+.

>> **Comorbidities parameters:** Lifestyle (tabagism, alcoolism), kidney disorders (eGFR…), metabolic disorders (diabetis, dyslipedemia, obesity), cardiovascular disorders (cardiac event, HTA event and treatments, CNS or peripheral vascular event), co-infection (VHC and/or VHB), CNS disorders (Neurodegenerative disorders) and cancer

Biobank

> The biotheque for the CO3 ANRS Aquitaine cohort has been constituted for 8 years, with an annual sampling for naive or on ART patients and a sampling at the time of the prescription of the first antiretroviral therapy

> This biotheque is set up the day of a usual consultation during the follow-up of the patients

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> Identification of **surrogate markers** for **CIA** and **IS**:
>> for **ART response** in treated patients
>> for **ART initiation decision** in naive patients (in particular those with CD4+ count >500mm^3)

> Possible associations between causes, types and consequences of immune activation could lead to the discovery of pathologic mechanisms that could be experimentally tested in vitro, and open new therapeutic strategies

> Finally this study is also of a general interest: pathologic pathways linking immune activation to comorbidities may concern chronic diseases related to senescence or chronic inflammatory diseases

Clinical development

> **Well-known sub-groups of HIV patients with comorbidities (CKD, Osteoporosis, Cancer, CNS or CV disorders):**
>> optimization of clinical studies (enrolment)
>> surrogate marker for CIA and IS validation
>> epidemiological studies to support market access on these sub-groups
>> definition of comorbidities preventive strategies

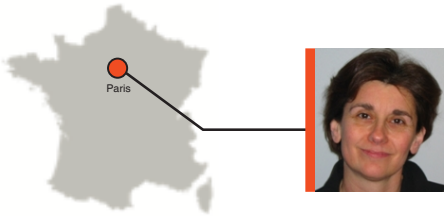
Outcomes research

> **Adjustment for associations between markers of activation, inflammation and senescence with comorbidities**

> Imputability of **antiretroviral drugs** in Renal function, bone mineral density, cancer and cognitive complications in HIV patients

> **Quality of life studies** of HIV patients with comorbidities

CKD-REIN :
Chronic Kidney Disease - Renal Epidemiology and Information Network



Dr. Bénédicte STENGEL
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OVERVIEW

AT A GLANCE

> Nephrology
> Chronic Kidney Disease (CKD)
> CKD patients
> Coordinated by Dr. Bénédicte Stengel
> Paris Sud University Sponsorship
> Funded by ANR, PHRC & Private funds

KEY FACTS & FIGURES

> Status: Inclusions started in July 2013
> 3 600 expected enrolled patients
> 150 included patients
> 5 years follow-up
> Multicentric cohort with 46 clinical sites and 4 renal care networks
> Blood, serum, plasma, DNA and urines biobanking
> Administrative database linkage expected with SNIIRAM databases

CKD-REIN cohort will served to improve our understanding of biological, clinical and health care system determinants associated with CKD progression and adverse outcomes. CDK-REIN collaborates also with CKDopps which allows to better understand international variations of CKD determinants.

CKD-REIN will foster CKD epidemiology and outcomes research and provide evidence to improve health and quality of life of CKD patients and the performances of the healthcare system in this field.

A total of 46 clinical sites and 4 renal care networks participate in the cohort. Stratified selection of clinical sites yields a sample that represents the diversity of settings, e.g., geographic region or public vs for-profit and non-for-profit private clinics.

Translational Research Clinical Development Outcomes Research

Positioning

> The CKD REIN project includes the French part of the international study called CKDopps (CKD Outcomes and Practice Patterns Study).

> The CKD-REIN study is the first large (N=3,600) cohort based on a representative sample of adult CKD patients receiving nephrologist-led care.

> CKD-REIN has already established a public-private partnership with 7 pharmaceutical companies.

LEADERSHIP

CKD-REIN's leadership team, led by Dr. B. Stengel, brings together renown epidemiologists and clinicians who have been committed to the field of CKD study and renal care for more than 20 years.

Dr. Bénédicte Stengel, Epidemiology/CKD, Research Director

- 20 years experience in the field of CKD epidemiology, principal investigator of many epidemiological studies on determinants and complications of CKD
- Co-investigator of other epidemiological studies and participation to various international consortia on prognostic evaluation of CKD and study of its genetic factors
- Elaboration of the "Renal Epidemiology and Information Network" registry protocol for renal replacement therapy managed by the Biomedicine Agency

Pr. Serge Briançon, Epidemiology/Patient-Reported Outcomes, Head of Public Health Division

- Relevant experience in the study of Chronic Diseases, Patient-Reported outcomes through epidemiologic and psychological approaches

Pr. Ziad Massy, Nephrology/Head of Nephrology Division

- Relevant experience in clinical research specifically focused on etiology and slowing of CKD progression, cardio-vascular complications in CKD, description of uremic toxin impact on CKD, CKD biomarkers and therapeutic trials

Pr. Christian Combe, Nephrology/Head of Nephrology Division

- Relevant experience in clinical research specifically focused on etiology and slowing of CKD progression, hemodialysis, nutrition and psychology

Pr. Denis Fouque, Nephrology/Head of Nephrology Division

- Relevant experience in clinical research specifically focused on slowing of CKD progression, bone quality in CKD, nutrition, hemodialysis and peritoneal dialysis, therapeutic trials and evidence-based medicine

Pr. Luc Frimat, Nephrology/Head of Nephrology Division

- Relevant experience in clinical research specifically focused on descriptive and analytical epidemiology of CKD, impact of CKD on patient quality of life, patient satisfaction, hemodialysis and peritoneal dialysis

SCIENTIFIC NETWORK & MANAGEMENT

- **CKD-REIN is linked with the international cohort CKDopps (coordination by Arbor Research, US)**

The French "branch" of the CKDopps cohort is coordinated by Pr C. Combe (CHU Bordeaux) and B. Stengel

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

The primary objective of the CKD-REIN cohort study is to develop a research platform to address key questions regarding various patient-level factors and biomarkers associated with CKD outcomes and to assess clinical practices and healthcare system-level determinants of CKD outcomes

Secondary objectives such as

> Assess the associations of a set of **psychosocial, environmental, biological, and genetic factors** and their interactions with several renal and non-renal outcomes

> Assess the value of new **biomarkers to predict CKD progression and outcomes**

> Evaluate the associations of a set of healthcare provider regarding **CKD management, healthcare organization and clinic services** offered to CKD patients with end-points such as **survival, ESRD* incidence, hospital admissions, patient-reported outcomes** and achievement of **clinical practice guidelines** at both national and international (CKDopps) levels

> Identify and quantify net costs of different treatment strategies and combine these with estimated practice effects on patient outcomes to provide estimation of incremental **cost-effectiveness ratios at both national and international levels**

*ESRD : End-Stage Renal Desease

INNOVATIVE SCIENTIFIC FEATURES

> Nationally representative sample of CKD patients

> Will provide an unbiased view of routine CKD care in a wide variety of settings while collecting standardized data

> The CKD-REIN research platform can serve for ancillary studies, in that prospect, innovative projects and broad use of data by external research groups will be encouraged

METHODOLOGY QUALITY

> A web-based data collection system was developed for CKD-REIN using the same secured web portal and patient identification module as the REIN registry

> Confidentiality, security and the integrity of data are covered by the Biomedicine Agency

> Serum, plasma, DNA and RNA are stored at ultra-low temperature at the Biobanque de Picardie, an ISO 9001 and NFS 96900 certified biological resources centre

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives : 3 600 patients CKD stage 3-4 receiving nephrologist-led care
1 800 stage 3 and 1 800 stage 4 patients

Sites : 46 nephrology clinics and 4 renal care networks. Clinical centres selection followed a stratification (e.g., based on survey data) to yield a sample that approximately represents the diversity of community-based nephrology clinics across the country

Inclusion criteria :
> eGFR between 15 and 60 ml/min/1.73m² for at least 1 month and no prior dialysis or transplantation
> Confirmed CKD

Exclusion criteria : <18 years old, prior dialysis or transplantation, pregnant, institutionalized, unable to give inform consent, decline participation

INCLUSION COLLECTION
Database: Clinical, biological, treatment, environmental and social data integrated through clinician/CRTs and self-reporting
Biobank: Blood, serum and urine sampling

FOLLOW-UP : ONCE A YEAR
Database: Combination of systematic follow-up visit with using a variety of different national administrative databases and sources to ascertain death and other health-related information (RNIPP, SNIIR-AM)
Biobank: Sampling follow-up will be at 1st, 3rd and 5th years

DATABASE & BIOBANK CONTENTS

Database

> **Patient-Level Variables - Medical Questionnaire (MQ), Interval Summary (IS), & Termination Form (TF)**

>> Patient characteristics: Demographics, cause of CKD…(MQ)

>> Medications: Medication categories: RAS antagonists, statins, phosphate binders, ESAs therapy… (MQ/IS)

>> Clinical measures: Blood pressure, weight, height, urine protein, biochemical measures…(MQ/IS)

>> Nutrition: Prescribed restrictions of protein, potassium, sodium and phosphorus (MQ/IS)

>> RRT planning: Vascular access referral, placement & procedures, services used (education programs, social worker, dietician), timing of decision about RRT modality, transplant wait-listing (MQ/IS)

>> Dialysis data: eGFR at dialysis initiation, clinical measures & dialysis dose (IS)

>> Clinical outcomes: Hospitalizations (IS), death (TF), study departure (TF)

> **Patient Questionnaire (PQ)**

Patient-reported data: QoL (KDQoL…), burden of kidney disease, functional status, self-reported depression (CESD), satisfaction with care, involvement in decision-making, using validated instruments when possible

> **Provider-Level Variables from Clinician Surveys (CS)**

>> Medical Director Survey: Clinic protocols for achieving practice guidelines (e.g., vascular access, kidney transplantation)

>> Physician practices not covered by protocol: Preferences for levels to initiate therapy and target for blood pressure, hemoglobine, phosphate, proteinuria - Treatment preferences, use of single vs. dual RAS antagonists…

>> Surveys of other health care providers: Nutrition, social work, vascular access, ESRD education programs; staffing levels; integration of care (multidisciplinary care clinic); palliative care services

> Expected linkage of the database with others databases such as SNIIRAM, RNIPP...

> No Imagery data collected

Biobank

> **Blood, serum and urine sampling**

>> At the inclusion and at 5 years follow-up for all patients

>> On 1 patient out of 3, sampling at 1 and 3 years follow-up

> 3 600 patients sampled at inclusion, 1 200 at 1 year and 3 years follow-up and 2 400 at 5 years follow-up, 40 ml of blood and 40 ml of urine per patient

> Samples are stored for 2/3 at -80°C and for 1/3 in liquid nitrogen for long time conservation

> Research on uremic toxins, CKD progression and complications biomarkers as well as large scale studies (-omics) will be feasible

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Identification of new biomarkers** to predict CKD progression and metabolic complications

> To carry out phamaco-genomic studies to characterize patient profile resistant to treatment

Clinical development

> **Validation of prognosis value of biomarkers** in various sub-populations defined by age, gender and diabetes status

> **Optimization of clinical studies** (variations in the prevalence and distribution of patient clinical and biological characteristics…)

> **Epidemiological studies** (prevalence and incidence of CKD-related outcomes and co-morbidities) to support market access

Outcomes research

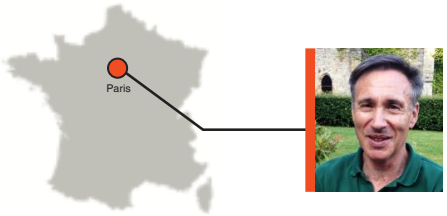
> **Pharmaco-epidemiological studies:** drug safety, “real-world” use, effectiveness, practice patterns, compliance, risk/benefit, adverse drug events of anti-hypertensive, lipid-lowering and antidiabetic drugs and of CKD-specific drugs (EPO ...)

> **Pharmaco-economic studies:** cost/benefit, health economic outcomes related to end-stage renal disease treatment : dialysis, transplantation, conservative management

> **Quality of life and patient satisfaction studies**

COBRA :
COHORT BRONCHIAL OBSTRUCION AND ASTHMA

COBRA



Michel AUBIER
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OVERVIEW

AT A GLANCE

> Immuno-inflammation
> Asthma & COPD
> Asthmatic and COPD patients
> Coordinated by Michel Aubier
> Inserm Sponsorship
> Inclusion ongoing
> Major Grants : Legs Poix, Inserm & private companies

KEY FACTS & FIGURES

> Status: Inclusion ongoing
> 2 000 asthmatic & 1 000 COPD expected patients
> 843 asthmatic patients & 242 COPD patients enrolled
> 10 years 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. Its originality relies on parallel follow-up of two cohorts. It also collects sample in biobank (serum and DNA). 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. This includes:

>> Determination, in details, of clinical phenotypes for asthmatic and COPD patients
>> Characterization of cellular and molecular phenotypes regarding to clinical phenotypes
>> Identification of early biomarkers of severity and progression associated with fixed airflow obstruction
>> Realization of clinical studies based on patients included in Cobra (Proof of concept or Phase II/III clinical trials)

Translational Research Clinical Development Outcomes Research

2008 First patient included
2014 04 Last patient included

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.

> Partnership with pharmaceutical companies are already ongoing.

LEADERSHIP

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

Michel Aubier, Head Pneumology department, Bichat Hospital, Paris

Director of the Clinical Investigation Centre Hôpital 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 AERES

Scientific evaluation & Committee Membership

>> Member of the « Conseil d'Orientation et de Réflexion Stratégique (CORES)» of the Inserm

>> Vice-Dean of the Faculty of Medicine Xavier Bichat (University Paris 7)

Current Collaborations

>> CPC/Helmholtz Center, Munich, Germany

>> Centre Nationale de Génotypage, Evry

>> Proteomic platform of Institut Jacques Monod, Paris

Nicolas Molinari, Associate Professor of Biostatistics, Montpellier 1 University, University Hospital of Montpellier

107 scientific publications (statistic and medicine)

Expertise

>> Expert for the National Clinical Research Program (PHRC) and the National Research Agency (ANR)

>> Scientific expert ANSM

>> Expert for the « Délégation à la Recherche Clinique et à l'Innovation » University Hospital of Montpellier

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)

Students supervising

>> Ph.D.: 11

>> Master: 32

SCIENTIFIC NETWORK & MANAGEMENT

Michel Aubier's Investigation Centre 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 to 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 8424 adult asthmatic patients

>> The **SITAX** study, by Michel Aubier, evaluated on 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)

>> Chitinase study in asthma and COPD: Expression and role of chitinases in asthma and COPD

Trough its Scientific Committee, COBRA implicates 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, multicentre, prospective, clinic-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 phenotyping, important step to provide dedicated personalized cares to patients

> In severe asthma patients, Cobra will allowed to identify clear biomarkers, better physiopathology understanding including genetic and epigenetics associated factors and assessment of future risks for patients

> At a glance, constituting biological samples banks in chronic airway diseases are unique chances to improve management, understanding, predict exacerbations and set-up early interventions based on biomarker identification and potential genetic susceptibilities

INNOVATIVE SCIENTIFIC FEATURES

> 5 years first follow-up phase with visit every 6 months and a second 5 years follow-up phase with visit every year

> Originality in cohort constitution

> Quality

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 Inserm dedicated unit

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	Expected enrolled patients are 2 000 asthmatic patients and 1 000 COPD patients
Sites:	14 clinics centres widespread in France
Inclusion criteria:	> Athsma: Men & Women, 18-80 years, smoker or non smoker athmatic patient, with or without reversibility on PFT (Pulmonary Function Tests) with well documented diagnostic of asthma > 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:	If the patient refuse 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: Blood and serum samples for future biomarker and -omic studies. In patients where invasive procedures are required, bronchoscopy allows to sample the Bronchoalveolar lavage (BAL) and bronchial biopsies

FOLLOW-UP :

> **EVERY 6 MONTHS (0 TO 5 YEARS)**

> **EVERY 12 MONTHS (5 TO 10 YEARS)**

Database: In addition to socio-demographic, environmental, and bio-clinical data, Concomitant treatments and health care provider recording, follow-up database record adverse events and serious adverse events

Biobank: Serum blood sample is done for serum collection at each follow-up visit

DATABASE & BIOBANK CONTENTS

Database

> Demographic: 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 moths) bronchial hyperresponsiveness test (COPD cohort), bronchial fibroscopy (COPD cohort)

> Therapeutic: Concomitant treatments

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

Biobank

> Blood samples have been collected for hematology and blood chemistry parameters and evaluation is done:

>> Asthma cohort: eosinophils, total IgE, specific IgE

>> COPD cohort: α1-antitrypsin, α1-antitrypsin genotype if required, erythrocytes, lymphocytes, eosinophils, monocytes, High sensitivity CRP

> Additionally a blood sample (with EDTA) for DNA extraction and 3 serum samples are obtained for constitution of DNA collection and serum collection. These samples are transferred from each site to the CRB Bichat Hospital for DNA extraction and serum collection.

> All samples are stored to CRB Bichat hospital at -80°C in a secure environment according to internal CRB procedures.

> This CRB is a certified organization with standard NF S95-900 (Ref. 2009/34457)

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RESEARCH COLLABORATION OPPORTUNITIES

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

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 steroidrefractory 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**

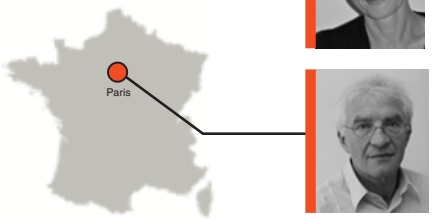
> Difference between asthmatic smokers and non-smokers on maintenance and reliever therapy

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

> **Comparative studies** to assess respiratory product efficiency

> **Quality of life studies**

CONSTANCES



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Pr. Lisa BERKMAN
Director, Harvard Center for Population and Development Studies

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OVERVIEW

AT A GLANCE

> Epidemiology
> General population
> Population-based cohort
> Coordinated by Marie Zins
> UVSQ Sponsorship
> Funded by ANR (PIA), Inserm, UVSQ and In–kind from CNAM

KEY FACTS & FIGURES

> Status: Inclusion and follow-up ongoing (more than35 000 sibjects already included)
> 200 000 subjects aged 18 to 69 years at inception
> Average rate of 40 000 subjects enrolled per year
> Follow-up period: 5 years
> Multicentric cohort
> Blood and urine biobanking
> Administrative database linkage (SNIIRAM, …)

Constances is a multi-purpose population-based cohort of 200 000 subjects representative of the French population aged from 18 to 69 years.

It is designed and managed to ensure a longitudinal follow-up over the longest possible period.

It will cover a wide range of personal, behavioral and environmental risk factors and health problems, notably chronic diseases and women's health, as well as disorders related to ageing, quality of life, sleep disorders, limitations and handicaps.

Translational Research Clinical Development Outcomes Research

Positioning

> Constances works closely with the German National cohort, the Biobanques Infrastructure and some French cohorts.
> Other similar general population based cohorts exist in Europe such as the German National Cohort (200 000 subjects), UK Biobank (500 000 people), LifeGene in Sweden and LifeLines in Netherlands.
> Constances is involved in BBMRI European Network, P3G international consortium, IDEAR consortium on aging in Europe.
> Constances coordinators are also responsible of the GAZEL cohort (20 000 people since 25 years) more than 50 projects carried out thanks to this platform and about 200 publications.
> A specific Public/Multi private Partnership has been designed. Its implementation is on going with several pharmaceutical companies.

LEADERSHIP

Constances's leadership team is set up with a team of renown epidemiologists, Marie Zins, Marcel Goldberg and Lisa Berkman, who are committed in the field during decades

Marie Zins, epidemiologist
Director of the Population-based Epidemiologic Cohorts Unit (UMS 011)

- PI of the Constances National Infrastructure
- Co-PI of the GAZEL Cohort
- Member of the National German Cohort Scientific Advisory Board
- Collaborations with numerous researchers in France and abroad

Lisa Berkman, epidemiologist
Director of the Harvard Center for Population and Development Studies

- Co-PI of the Constances cohort
- Member of the Scientific Committee of several cohorts in the USA and other countries
- Collaborations in the USA, Europe and France

Marcel Goldberg, epidemiologist
Professor od Epidemiology

- Initiator of the GAZEL cohort in 1989
- Co-PI of the Constances cohort
- Coordinator of the Information Systems of the High Council of Public Health
- Member of several scientific committees

SCIENTIFIC NETWORK & MANAGEMENT

Constances works in close collaboration with other European population-based cohorts
- >> Strong partnership established with the German National Cohort (200 00 subjects) for harmonizing data on exposures and clinical endpoint
- >> Participation to the IDEAR (Integrated datasets across Europe for Ageing Research) consortium
- >> Part of the BBMRI-LPC consortium associating European "mega cohorts" in UK, Germany, Netherlands, Finland, Sweden...

Constances is collaborating with other French cohorts on specific pathologies i.e.
- >> CKD REIN on Chronic Kidney Disease, Haguenau on diabetes…

Constances is collaborating with other population-based cohorts in France
- >> COSET Cohort (National Institute for health Surveillance)

Constances also participates in the following international consortiums
- >> The P3G : Public Population Project in Genomics
- >> BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) and BBMRI-Large Prospective Cohorts

Constances is involved in European projects (FP7, ERA Age, H2020…)

Constances Scientific team is composed of the following experts
- >> **Nutritionist:** Sébastien Czernichow, MD
- >> **Epidemiologist:** Matthieu Carton, MD and Annette Leclerc
- >> **Psychiatrist:** Cédric Lemogne, MD
- >> **Occupational Health:** Alexis Descatha, MD
- >> **Biologist:** Joseph Henny

Constance Scientific Committee is composed of the following international experts:
- >> **Aging:** Sandrine Andrieu, Inserm/Toulouse III University France
- >> **Public Health:** Marc Brodin, Paris VII University France
- >> **Demography of aging:** Emmanuelle Cambois, INED Paris France
- >> **Biobanking:** Bruno Clément, Inserm Rennes France
- >> **Epidemiologic surveillance:** Jean-Claude Désenclos, InVS, Saint Maurice France
- >> **Data harmonization:** Isabel Fortier, McGill University Montreal
- >> **Environmental epidemiology:** Denis Hémon, Inserm Villejuif France
- >> **Cancer Epidemiology:** Rudolf Kaaks , German Cancer Research Center, Heidelberg Germany
- >> **Health economics:** Victor Rodwin, Robert F. Wagner Graduate School of Public Service, New York USA
- >> **Cancer Epidemiology:** Rodolfo Saracci, CIRC Lyon France and Jack Siemiatycki, Montréal University Canada [Chairman of the Scientific Committee]
- >> **Social sciences:** Roxane Silberman, CNRS Paris France
- >> **Exposure assessment:** Roel Vermeulen, IRAS Utrecht University Pays Bas
- >> **Cancer and aging:** Elisabete Weiderpass, Karolinska Institutet, Stockholm, Sweden and Cancer Registry of Norway, Oslo Finlande, Norvège, Suède

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Constances is a large population-based general-purpose observational prospective cohort managed as a National Infrastructure that will contribute to the development of epidemiologic research and to provide useful public health information

Constances is an “epidemiologic laboratory” open to specific “nested” ancillary research studies from either, academic or private, French and international research community

Constances provides new information on the impact of major determinants of health in the French population providing a sound base for targeted prevention

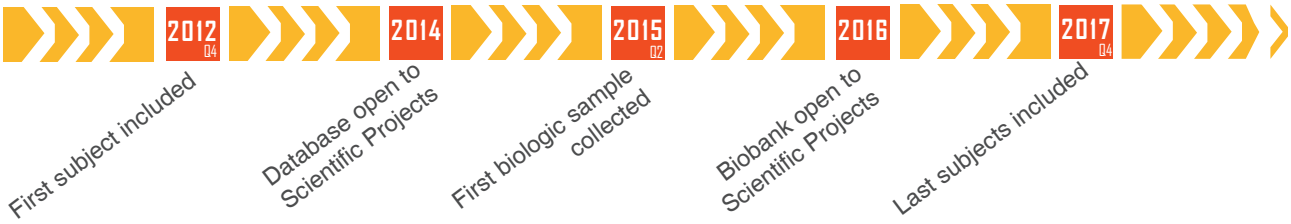
INNOVATIVE SCIENTIFIC FEATURES

> Representative of the French adult population
> Identification of prevalent and incident diseases among the participants and ascertainment of diagnosis (cardiovascular events, cancers and neurodegenerative diseases)
> Comprehensive data on health care, prescription drugs and medical devices
> Linkage with national administrative databases (SNIIR-AM, CNAV, causes of death)

METHODOLOGY QUALITY

> Representativeness of the cohort ensured thanks to the randomly selected control-cohort of non respondents (n=400 000)
> Prospective follow-up of this control-cohort for health and social characteristics in administrative databases
> Deep experience in database management with high security
> High-level of bioclinical databases with intra- and inter- “Health Screening Centers” standardization and SOP implementation
> Permanent quality control program by independent provider

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives:	200 000 subjects aged 18 to 69 years at inclusion. The source population is that of the people in France whose health insurance is administered by the CNAMTS. This fund covers more than 85% of the French population
Sites:	17 Health Screening Centers (HSC) HSC located across the country and equipped to collect biomedical data
Recruitment Target:	Inclusion of the entire cohort over a 5 year period. 5 Annual waves of 20 000 to 60 000 subjects
Data collection: **through Health Examinations and questionnaires**	**Social and demographic characteristics:** work status and situation, education level, marital status… **Health data:** incident and prevalent diseases, self-reported health and quality of life scales, personal and family history (cancer, cardiovascular, psychiatric), cause of death. **Health problems specific to women:** Treatment for menopause, osteoporosis and osteoporotic fractures, infertility and delayed childbearing, sexual transmitted diseases and issues related to sex life … **Behaviors:** Smoking and alcohol consumption, dietary habits and physical activity, marijuana use and sexual orientation. **Occupational factors:** Job history, lifelong and current occupational exposure to chemical, physical and biological agents, postural, mechanical and organizational constraints and stress at work.

INCLUSION COLLECTION

Questionnaires: Health & lifestyle, job history, women's health, working conditions and occupational exposures

Health Examination in HSC: + physical and cognitive functional assessment for 45 years old and over Administrative national databases (SNIIRAM; PMSI; CNAV; Cause of death): health care use, hospital discharge records, mortality

Biobank: Biological samples: serum, plasma and urine collected during health examination

FOLLOW-UP :

Annual self questionnaire: Health status life events, smoking, alcohol,

Health Examination in HSC: every 5 years regular linkage with national administrative databases

Biobank: Biological samples: serum, plasma and urine collected during health examination

DATABASE & BIOBANK CONTENTS

Database

>> Health data, use of care data, health examination results, socio-demographic characteristics as well as behavioral and occupational information. These data will be organized in 5 themes: "**Senior Health & Ageing", "Women's Health", "Oncology", "Cardio - respiratory, inflammatory and metabolic diseases", "Behaviors & Environment"**

>> Collection specificities: functional physical and cognitive capacities assessments every 5 years for people aged 45 years and older

>> For each subject, personal health and social data from the national health and socioeconomic **databases (SNIIRAM and PMSI)** are linked to data collected from Constances questionnaires and health examination. This l**inkage is already fully operational**

>> Other type and specific of data, like imagery data, will be collected under specific scientific projects which can be performed on part of the subjects sample

Biobank

>> Blood and Urine, starting from the beginning of 2015

>> 100 000 subjects will be sampled for a total of 10 aliquots per subject

>> Other material specimens (stools,…) if additional budget from public/private partnership can be collected

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Neuropsychological testing** as young as 45, allowing for predicting future neurodegenerative diseases during follow-up

> Study of the **role of obesity** on respiratory chronic diseases and Alzheimer disease

> Definition of a **validated measure** of frailty among aging subjects

Clinical development

> Use of **biochemical markers** of liver fibrosis for mass screening

> Estimation of disease and risk factors prevalence for numerous conditions

Outcomes research

> Estimation of the incidence of **drug-induced liver** complications at an early stage and identification of new associated risk factors

> Description of **the use of drugs in real life,** observance and practice patterns for several chronic diseases (diabetes, asthma…**)**

> Estimation of the **economic burden** of several chronic diseases (diabetes, asthma…) including medical costs and impact on employment

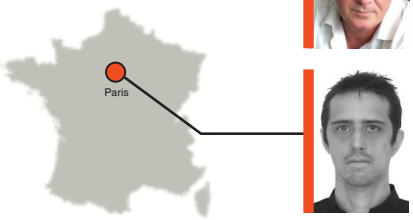
> Impact of chronic diseases on **Quality of Life**

Public-Private partnership interest:

Due to the large coverage of health conditions and the wealth of data collected for a very large representative sample, Constances should be of interest to companies of the health (Pharmaceutical, Diagnostic, Medical Devices, equipment suppliers…)

COPANFLU :
COHORTS OR PANDEMIC INFLUENZA

aviesan
ITMO Santé publique



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Rosemary DELABRE
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OVERVIEW

AT A GLANCE

> Infectious diseases
> Pandemic Influenza
> General Population
> Coordinated by Fabrice Carrat
> AP-HP Sponsorship
> Funded by ITMO Infectious diseases, ITMO Public Health, the French Ministry of Health, French Ministry of Research

KEY FACTS & FIGURES

> Inclusion and follow-up completed
> 601 households corresponding to 1 450 individuals
> Follow-up for 2 years (2 flu seasons)
> National multicentric cohort
> Biobank: blood samples at each visit for all patients; In case of influenza-like symptoms, additional blood sample + throat swab + stool sample

The main objective of **CoPanFlu** was to determine the risk of infection by the H1N1 pandemic influenza virus.

An integrative multidisciplinary approach was used to extensively characterize the various determinants of risk:
>> Epidemiological and environmental
>> Immunological (including serological status and genetic markers of immunity)
>> Virological

The large amount of data collected throughout a longitudinal follow-up of households and individuals, including biological samples, allows integrative analysis of complex phenomena such as risk factors of influenza infection in the general population and determinants of response to infection or vaccination.

Translational Research Clinical Development Outcomes Research

Positioning

> CoPanFlu is a rather unique cohort assessing the risk for influenza infection because of its fully integrative approach

> First attempt to thoroughly study determinants of infection by respiratory viruses in a large randomly selected sample of households

> Copanflu is part of a larger international consortium involving other countries beyond France: Mali, Bolivia, Laos and Djibouti.

LEADERSHIP

Pr. Fabrice Carrat, MD, Ph.D.
Senior lecturer in Epidemiology of Infectious Diseases, Inserm / UPMC

Medical Degree in Public Health and PhD in Biomathematics

Professor in Public Health and Public Health practitioner at Saint-Antoine Hospital, AP-HP, Paris.

Author of studies in epidemiology of infectious diseases since 1992

Research interests include influenza and viral hepatitis epidemiology and modelling, and methods in epidemiology.

Network

>> Member of the French National Public Health Committee (Haut Conseil de la Santé Publique)

>> Member of the French National Clinical Research Committee

>> Member of the public health expert panel on influenza pandemic planning

Experience in steering major clinical epidemiology projects

>> Therapeutic or cohort studies: coordinated 5 thematic or general population cohorts and 3 randomized intervention trial as Principal Investigator

>> Heads clinical data and monitoring center in partnership with the French National Agency on AIDS and Viral Hepatitis (ANRS)

>> Supervision of the methodology, epidemiological scientific issues, data and monitoring of 15 clinical trials or epidemiological studies

180 publications mostly on influenza and viral hepatitis

Dr. Nathanaël Lapidus, MD, Ph.D.
Lecturer in Epidemiology and Biostatistics, Inserm / UPMC

Medical Degree in Public Health and PhD in Epidemiology

Public Health practitioner at Saint-Antoine Hospital, AP-HP, Paris

Author of studies in epidemiology and modeling of infectious diseases since 2005

Rosemary Delabre, MPH
Doctorant, Inserm / UPMC

Master of Public Health, specialization in epidemiology

Thesis topic: «Immune Correlates of Clinical Protection in Influenza »

SCIENTIFIC NETWORK & MANAGEMENT

CoPanFlu-France served as a blueprint for the other international cohorts developed in the CoPanFlu International Consortium, consortium between the French National Institute of Health and Medical Research (INSERM), the Institute of Research for Development (IRD) and the Mérieux Fondation under the promotion of the School of Advanced Studies in Public Health (EHESP)

Prospective cohorts of households followed for 2 years in:

>> **Mali**[1]: The CoPanFlu-Mali programme studied a cohort of 202 individuals living in the rural commune of Dioro (southern central Mali)

>> **Réunion Island**[2]: The CoPanFlu-RUN cohort enrolled a total of 2,164 individuals from 772 households

>> **Laos**[3]: CoPanFlu Laos is a general population cohort of 807 households and 4,072 participants established in March 2010

>> **Djibouti**[4]: CoPanFlu study was established in Djibouti from the four city administrative districts, enrolling 1045 subjects from 324 households

>> **And Bolivia**: unpublished data

Through its Scientific Committee, CoPanFlu implicates experts in:

>> **Genetics:** Laurent Abel, Inserm U550, Paris, France

>> **Virology:** Laurent Andreoletti, Laboratoire de virologie médicale et moléculaire, EA-4303, Reims, France; Marianne Leruez-Ville, Laboratoire de virologie Necker, EA 3620,PARIS, France

>> **Modeling:** Pierre-Yves Boelle, Inserm U707, Paris, France; Simon Cauchemez, Imperial College, London, UK

>> **Virology & biobank:** Xavier de Lamballerie, UMR190, Marseille, France

>> **Immunology:** Marie-Lise Gougeon, Institut Pasteur, Paris, France; Eric Vivier, Inserm U631 / CNRS (UMR 6102), Marseille, France

>> **Environmental health:** Michele Legeas, EHESP, Rennnes, France; Pierre Le Cann, EHESP, Rennnes, France

>> **Risk perception:** Michael Schwarzinger, U912 Marseille, France; Michel Setbon, CNRS UMR 6123 / EHESP, Aix-en-Provence, France

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PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

To study the risks and characteristics of influenza infections

To assess, through an integrative approach considering a complex combination of data, various determinants of risk such as:
> Epidemiological, behavioral and environmental
> Immunological determinants, including genetic immunity components
> Virological determinants, transcriptomes

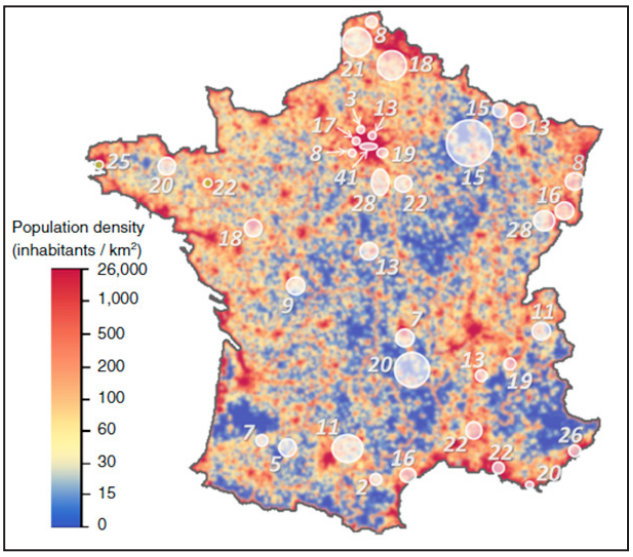
To provide researchers with a comprehensive clinical and biological database; a valuable resource for information pertaining to viral infection and immunological response to respiratory viruses

INNOVATIVE SCIENTIFIC FEATURES

> Copanflu has an original design based on a representative sample of households from the general French population
> Data is collected on all household members, with biological samples and environmental data (ie. household geolocalisation)
> Massive amount of data collected allowing to carry on many studies in various medical fields

METHODOLOGY QUALITY

> Very thorough sampling scheme, obtaining a representative sample of the French general population
> Data collection by dedicated and trained nurses
> Weekly surveillance during winter seasons (IVRS)
> State of the art collection, processing and storage of biosamples
> High quality data-management



Distribution on included households in relation to density of population (total: N=601)

White discs represent the 40 areas of the study. Overlapping areas are merged

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	2 100 subjects, providing 80% power to detect covariates associated with a relative risk of infection RR >1.4, assuming a cumulative incidence of 10%
Sites:	A total of 601 household participated in the study, resulting in data collection for a total of 1 450 subjects
Inclusion criteria:	All randomly selected households are eligible. All household members are eligible to participate in the study, regardless of age. Written informed consent.
Exclusion criteria:	Non-french speaking individuals. Households without an adult member (>18 years old)

INCLUSION COLLECTION

Database: medical history, vaccination, preventive measures against influenza, socio-demographic data, characteristics of housing, geographical area characteristics, attitudes, beliefs and risk perception

Biobank: Blood sample drawn for serological analyses. Heparinated tube for cellular immunity analysis, blood sample for transcript analysis

FOLLOW-UP :

> **SYSTEMATIC ANNUAL STUDY VISIT**
> **WEEKLY TELEPHONE SURVEILLANCE FOR ILI EVENTS**
> **ILI STUDY VISITS AND VACCINATION VISITS if necessary**

Database: Collection or update individual and environmental data on questionnaires

Biobank: Serum blood sample collection at each follow-up visit

DATABASE & BIOBANK CONTENTS

Database

>> **Sociodemographic characteristics and medical history:** age, sex, number of subjects and children in the household, socio-professional category of the head of the family, professional occupation, history of chronic disease, pregnancy, current or former smoker, history of ILI for seasons 2006-2007 to 2009-2010, medical history and habits of other subjects of the household

>> **Geographic area:** surrounding activity, demography

>> **Preventive measures:** vaccination, hygiene measures, vaccination status of other subjects in the household, hygiene measures of other subjects of the household

>> **Housing characteristics:** general characteristics, presence of animals, number of rooms, type of heating

>> **Duration of meetings:** by location (home, work, school, transport) , by age of contacts

>> **Attitudes, beliefs and risk perception**

Biobank

>> **Inclusion and Systematic annual visits:** blood samples from all household members

>> Blood samples are collected and centralized for serological analyses. For subjects older than 10 years, a heparinated tube was also collected to study cellular immunity, as well as a blood sample dedicated to transcript analyses.

>> **Influenza-like illness (ILI) visits:** nasal swabs collection and throat swab sampling for all household subjects. For symptomatic subjects over 10 years, a stool sample and blood sample were collected (blood sample collected to study innate immunity against influenza and the related transcriptome)

>> **Vaccination visits:** in order to update serological information, a blood sample was collected from subjects who had an influenza vaccination, between 2 and 4weeks following this vaccination.

>> **Biobank contains:** 5 443 blood samples + 1 300 nasal swabs + 638 throat/stool swabs + 1 110 DNA samples for 1 451 subjects

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Publications in progress

>> **Risk factors of influenza A/H1N1 in a prospective household cohort in the general population: results from the CoPanFlu-France cohort**

>> **A causal model to explore the relative influence of viral exposure and host susceptibility on the risk of influenza virus infection; findings from a household cohort**

RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Determinants of the immune response to infection or vaccination**

> **Study innate immunity against influenza and the related transcriptome**

> **Modelling study** to predict second pandemic season and its need

Clinical development

> **Identify determinants of vaccination against influenza**

> **Identify factors associated with a high anti-H1N1pdm serological titer**

> **Identify risk factors associated with influenza infections:**
>> For the first pandemic season: based on serological data
>> For the following seasons: on both serological and virological data

> **Influence of viral exposure and host susceptibility on the risk of influenza virus infection**

Outcomes research

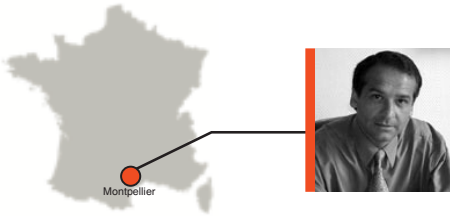
> **Social science and risk perception**

> **Trends in influenza vaccination behaviours:**
>> Study of variations in vaccination behaviours
>> Sociodemographic characteristics associated with vaccination behaviours

> **Collective and environmental risk factors of infection**

ESPOIR :
Etude et Suivi des POlyarthrites Indifferenciees Recentes

aviesan
ITMO Santé publique



Bernard COMBE
Professor of University - Hospital Practitioner, Head of the bone and joint department, Montpellier University Hospital

http://lacohorteespoir.fr

OVERVIEW

AT A GLANCE

> Immunology
> Rheumatoid arthritis
> Undifferentiated arthritis or rheumatoid arthritis patients (<6 months disease duration)
> Coordinated by Bernard Combe
> French Society of Rheumatology sponsorship
> Funded by INSERM, French Society of Rheumatology & private companies

KEY FACTS & FIGURES

> Status: Inclusion closed, follow-up ongoing
> 813 enrolled patients
> 20 years follow-up
> Multicentric cohort with 14 regional centres
> Serum, DNA, urine, white blood cells synovium liquid and tissue (when possible) biobanking

ESPOIR cohort study is a large national multicentre, longitudinal and prospective cohort, which aims to set up databases to allow various investigations on diagnosis, prognostic markers, epidemiology, pathogenesis and medico-economic factors in the field of early arthritis (less than 6 months disease duration) and rheumatoid arthritis. Clinical, biological, radiographic and medico-economic databases have been constituted to fit in the different objectives of the project and more than 20 scientific studies have already been accepted by the scientific committee.

Specific objectives are in the following domains:

>> **diagnosis:** to help to determine among clinical, biological, radiographic and immunogenetics parameters those allowing the earliest diagnosis classification as possible, in order to target early therapy.

>> **prognosis:** to early identify those patients at risk of severe disease by investigating among clinical, radiological, biological, genetic and sociologic factors.

>> **medico-economic:** to identify the costs and their determinants at various disease stage.

>> **pathogenic:** to collect a databank of sera, DNA, RNA, synovial fluids and tissues in order to allow various studies on RA pathogenesis including transcriptoms and other genomics.

Translational Research Clinical Development Outcomes Research

Positioning

> ESPOIR Cohort is collaborating with several other European and Canadian Cohorts and mainly the LEIDEN cohort (NL), which is with ESPOIR Cohort, a major international cohort in early arthritis.

> ESPOIR has contributed to the development of classification criteria and remission criteria for RA.

> ESPOIR has already established partnerships with 7 pharmaceutical and diagnostic companies.

LEADERSHIP

Bernard Combe, Rheumatology,
Professor of University - Hospital Practitioner,
Head of the bone and joint department, Montpellier University Hospital

Principal Investigator and coordinator of 2 national multicenter cohorts in Early Arthritis

Member of the steering committee of one national multicenter spondyloarthritis cohort

Chairman of the national guidelines for the management of Rheumatoid Arthritis:

>> HAS (2007)
>> French Society of Rheumatology (2007,2013)
>> Chairman of the European Guidelines for the management of Early Arthritis (2007)

Numerous European and north American collaborations in the field of RA and early arthritis

Jean-Pierre Daures, Epidemiology
Professor of University - Hospital Practitioner,
Head of the epidemiology and biostatistic department, Nimes university Hospital

Co-coordinator of 2 national cohorts of patients with chonic arthritis and spondyloarthritis

Scientific chaiman of 2 regional Cancer registries

Member of the HAS committee on cancer screening

Several national collaborations in the field of chronic diseases and cancers

SCIENTIFIC NETWORK & MANAGEMENT

ESPOIR closely workswith European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) taskforce aiming to define RA-specific classification criteria notably erosiveness

So, it works with other international cohorts in RA such as:

>> Leiden cohort lead by T. Huizinga and D. van der Heiden
>> Norfolk Arthritis Register lead by D Symmons
>> 6 other European cohorts & 2 Canadian cohorts

Through its Scientific Steering Committee, ESPOIR implicates experts in RA localized in France:

>> F. Berenbaum (Paris St Antoine)
>> P. Boumier (Amiens)
>> A. Cantagrel (Toulouse)
>> G Chiocchia (Paris-Inserm)
>> B. Combe (Montpellier)
>> JP. Daures (Nimes)
>> M. Dougados (Paris Cochin)
>> P. Goupille (Tours)
>> F. Guillemin (Nancy)
>> R.M. Flipo (Lille)
>> X. Le Loet (Rouen)
>> X. Mariette (Paris Kremlin-Bicetre - Chairman from june 2013 to june 2015)
>> O. Meyer (Paris Bichat)
>> Ph. Ravaud (Paris Hotel Dieu)
>> A. Saraux (Brest)
>> T. Schaeverbeke (Bordeaux)
>> J. Sibilia (Strasbourg)
>> O. Vittecoq (Rouen)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

The primary objective is to set-up a multicentre cohort of early arthritis (less than 6 months disease duration) in France that could serve as a database to studies of various natures

Specific objectives are in the following domains:

> **Diagnosis:** to help to determine among clinical, biological, radiographic and immunogenetics parameters those allowing for earliest diagnosis classification as possible, in order to target early therapy

> **Prognosis:** to early identify those patients at risk of severe disease by investigating among clinical, radiological, biological, genetic and sociologic factors

> **Medico-economic:** to identify the costs and their determinants at various disease stage

> **Pathogenic:** to collect a databank of sera, DNA, RNA, synovial fluids and tissues in order to allow various studies on RA pathogenesis including transcriptoms and other genomics

Specific objectives are in the following domains:

> **Safety:** to monitor adverse events, particularly rare drug adverse events, in collaboration with other international studies

> **Research platform:** to allow access to the data collected in this cohort study in order to facilitate new projects submitted to and approved by the scientific committee

> **Continuous medical education:** to set up an educational program for the general practioners (GPs) focus on early arthritis and early referral recommendations

INNOVATIVE SCIENTIFIC FEATURES

> National cohort dedicates to very early arthritis
> The largest early arthritis cohort with large database
> Get access to patients followed by a network of private rheumatologists
> National scientific committee (meeting every 6 months)
> Central data management & quality control

METHODOLOGY QUALITY

> Quality charter approved by each clinical site
> Patients have been followed every 6 months during the first 2 years then every year during at least 10 years

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives: Using intermediate estimates, it would be necessary to start with 400 RA patients. Given the probability that 50% of patients will probably not turn into rheumatoid arthritis after 2 years, it was planned to include 800 early arthritis patients

Sites: 14 regional centres

Inclusion criteria:

> Patients aged over 18 and under 70
> Clinical diagnosis of rheumatoid arthritis as certain or probable or clinical diagnosis of undifferentiated arthritis potentially becoming RA
> At least 2 inflammatory joints since 6 weeks: a swollen joint has to be observed in two joint sites and be present since at least 6 weeks
> Arthritis starting since less than 6 months
> Never prescribed DMARDS, corticoids, except if less than 2 weeks or except intra-articular injection less than 4 weeks before inclusion. Corticosteroids may be authorized if prescribed for 2 weeks or less at least 2 weeks before the inclusion and with a maximum mean dosage of 20 mg/day prednisone

Exclusion criteria:

> Other inflammatory rheumatisms or connective tissue diseases clearly defined.
> Early arthritis with no potential chance to become RA

INCLUSION COLLECTION
Database: Clinical (including standard biology) data and medicoeconomic data
Biobank: Serum, DNA, urine, white blood cells synovium liquid and tissue (when possible)

FOLLOW-UP:
> **EVERY 6 MONTHS DURING THE FIRST 2 YEARS**
> **THEN EVERY YEAR DURING AT LEAST 10 YEARS**
Database: Clinical (including standard biology) data and medicoeconomic data
Biobank: Serum and urine were also obtained at each follow-up visit

DATABASE & BIOBANK CONTENTS

Database

>> **A large database has been constituted to fit in the different objectives of this project.** It includes clinical (including standard biology) and medicoeconomic data collected and computerised at each visit in each centre, then centralised at the coordinating centre (Montpellier)

>> **Comorbidities:** HTA, Hypercholesterolemia, Hypertriglyceridemia, Myocardial ischemia, Stroke, Lymphoproliferative disorder, Cancer, Gastro-intestinal event, Diabetes, Thyroid disorder, Tuberculosis, HIV infection, Hepatitis, Hepatitis C

>> **Clinical and biological evaluation:** Baseline CRP (N < 10 mg/l), IgM and IgA rheumatoid factor and anti-CCP2 antibodies were performed for all the patients using the same technique in a central lab. HLA DRB1* genotypes were determined in each centre

>> **Imaging:** X-ray database included at baseline a chest X-ray, both hand and wrist antero-posterior view and forefoot. At each follow-up visit hand, wrist and foot X-ray were collected as well as other painful joints if necessary. All original X-rays were stored in the radiological coordinating centre (Brest). Ultrasonography and Magnetic Resonance Imaging were performed on hands and feet in selected centres.

>> **Quality of life:** questionnaires including HAQ, SF36, Euroqol and AIMS-2 short form and a medicoeconomic questionnaire

Biobank

>> Biological database comprised an agreed-on list of routine investigations
>> Serum, DNA, urine, white blood cells synovium liquid and tissue (when possible) were collected at baseline
>> Serum and urine are also obtained at each follow-up visit
>> They are sent and double stored in adequate and definite conditions in the biological coordinating centre (Paris-Bichat)

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Genotype-phenotype correlation analysis** and gene-environment interaction study in early rheumatoid arthritis
> **Identification of biomarkers:**
>> IL-2RA and IL-2RB genes (erosive status)
>> Secreted phosphoprotein 1 gene (RA susceptibility gene)
>> Markers of B-lymphocyte activation (disease activity)
>> Serum level of adiponectin (radiographic disease progression)
>> Dickkopf-1 (Structural Progression)
> Autoantibodies to citrullinated fibrinogen compared with anti-MCV and anti-CCP2 antibodies in diagnosing rheumatoid arthritis at an early stage

Clinical development

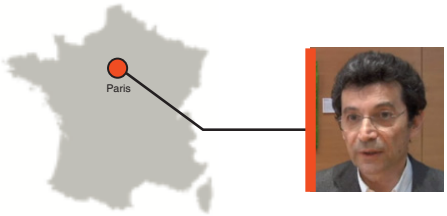
> **Management of early arthritis:**
>> Hormonal replacement therapy and risk reduction for RA in women with early arthritis who carry HLA-DRB1 *01 and/or *04 alleles by protecting against the production of anti-CCP
>> Radiographic Progression as a predictor of further Progression in Early Arthritis
>> Erosions detect in early arthritis
> **Risk Factors identification:**
>> Cigarette smoking and PR
>> Cardiovascular risk factors linkage with inflammation
>> Risk model of rapid radiographic progression
> **Disease progression:** Predictors of radiographic progression
> **Definition of rheumatoid arthritis classification criteria**
> **Validation of ACR/EULAR Definition of Remission**

Outcomes research

> Bests practices definition in the management of early arthritis:
>> **Benefits** of ultrasonography
>> Factors determining a **DMARD initiation**
>> **First-line Disease Modifying Antirheumatic Drug**
>> **DAS-driven therapy versus routine care**
>> **Routine viral screening** utility
>> Baseline laboratory test abnormalities
> Medico-economic studies: Early referral to the rheumatologist, work productivity loss, evolution of direct costs in the first years of rheumatoid arthritis
> Quality of life: Comparison between the EQ-5D and the Short Form 6D utility

FAST:
Fight Ageing and STress

University Hospital Department – DHU
FAST
Fight Aging and STress



Pr. Jean MARIANI
MD, Ph.D., University Hospital Physician and Professor of Cell Biology Director of the Neurobiology of Adaptative Processes Unit and Head of Clinical Physiology Unit at Charles-Foix Hospital

Christian.neri@inserm.fr

OVERVIEW

AT A GLANCE

> Elderly diseases
> Pathologies associated with aging
> Aged patients +70 years, possibly younger patients
> Coordinated by Pr. J. Mariani in collaboration with Dr. C. Neri, Pr. J. Boddaert, Pr. M. Verny and Pr. E. Pautas
> AP-HP Sponsorship
> Funded AP-HP

KEY FACTS & FIGURES

> Status: Inclusion & follow up
> Continuous inclusion
> Already enrolled patients:
>> UPOG: 700
>> COGDISCO: 800
> Follow-up for 5 to 10 years and more
> National multicentric (possibly international)
> Biobank: blood, serum, plasma
> Administrative database linkage with PMSI (national public health-care data)

Major aim is to enable exploitation of information for medical intelligence in stress response and age-related diseases through a unified framework covering care and research.

FAST originality relies on Cluster of cohorts with deep phenotyping for well defined and practicable clinical scenarios (cross sectional/longitudinal) supported by infrastructure and core facilities

>> UPOG: patients in perioperative management. Aim is to precisely describe and analyze comorbidities, complications and outcomes in the field of surgery with a one-year follow-up, and weight of theses factors on prognosis.

>> CogDisCo: patients with cognitive disorders (frequently due to neurodegenerative disease). Aim is to describe and analyze the role of comorbidities on presentation and course of cognitive disorders.

>> AGER: patients hospitalized in acute geriatrics. Aim is to precisely describe comorbidities, complications and outcomes in the field of acute medical conditions with a one-year follow-up, and weight of theses factors on prognosis.

>> Hundreds of +70-year patients have been followed, Design enabling heterogeneous data (clinical, biological, functional/brain imaging, 'omics/NGS) to be collected and analyzed.

Secondary objectives are:

>> Strategic alignment with international partners and cohorts (project expansion, new projects, replication studies)
>> Transfer of knowledge to less aged population (partnerships)
>> Enable human iPS cell research in stress response

Translational Research Clinical Development Outcomes Research

Positioning

> FAST is under discussion to collaborate with French or International cohorts in the field of aging
> FAST is implicated in European KIC (Knowledge and Innovation Communities) project dedicated to Healthy Living and Active Ageing and under discussion for H2020 project submission
> FAST is also closely collaborating with epidemiologic projects in Medication in AD patients and modeling in presymptomatic HD patients

LEADERSHIP

COORDINATOR

Pr. Jean Mariani, MD, Ph.D., University Hospital Physician and Professor of Cell Biology
Director of the Neurobiology of Adaptative Processes Unit and Head of Clinical Physiology Unit at Charles-Foix Hospital

He is expert in neural development and ageing, not only in experimental models but also functional examination of elderly patients and implementation of new tests of the episodic memory focusing.

He has lead the interdisciplinary CNRS program «Longevity and Aging". He is member of the Directoire de la Recherche of UPMC and has published +200 scientific papers.

VPS RESEARCH

Dr. Christian Neri, Ph.D.
Research Director at Inserm, Head of Neuronal Cell Biology and Pathology group at CNRS UMR8256

He is an internationally recognized expert in neurodegenerative disease biology and genome science

Coordinator of the Centre for Translational Research on Ageing (CTRA), Coordinator of Inserm Associated International Lab 'Neuronal Longevity' with the Univ. of Montreal and Buck Institute, Member-elect of Euro-HD Executive Committee

VPS CARE

Pr. Marc Verny, MD, Ph.D.
Pitié-Salpêtrière hospital, Paris

He is expert in cognitive exploration, care and dementia studies in elderly patients and also in frequent neurological disorders as stroke, epilepsia, parkinson

Pr. Eric Pautas, MD, Ph.D.
Charles Foix hospital, Paris

He has internationally recognized expertise in using anticoagulation drugs in the elderly

Pr. Jacques Boddaert, MD, Ph.D.
Faculty Professor of Geriatrics, Head of UPOG unit, Pitié-Salpêtrière hospital

He is expert in taking care of elderly patients in emergency medicine and in the field of surgical pathologies

SCIENTIFIC NETWORK & MANAGEMENT

FAST is already built around and/or contributing to large research networks:

>> Within the frame of the **iHD project,** a network of knowledge managers and users that brings together key players in the field of medical intelligence (e.g. Euro-HD Network)

>> Within the **EIPAHA project** (European innovation partnership on active and healthy ageing) under the heading «Integrated Care", which aims to increase the average healthy lifespan by two years by 2020 by bringing together key stakeholders (end users, public authorities, industry)

>> Within the newly developing national network on ageing that is linked to the **European Horizon 2020 KIC initiative on "Healthy Life and Active Ageing"**

FAST team is also collaborating with Buck Institute for Research on Aging and Northwestern University, Buehler Center on Aging, Health & Society in USA

The Scientific Sommittee comprises :

>> J. Mariani, MD, Ph.D., aging, neurobiology
>> C. Neri, Ph.D., neurodegenerative disease, stress response, genome science, systems modeling
>> M. Verny, MD, Ph.D., cognitive disorders and aging, clinical research
>> J. Boddaert, MD, Ph.D., perioperative medicine, clinical research
>> J. Belmin, MD, Ph.D., geriatrics, clinical research
>> E. Pautas, MD PhD, geriatrics, clinical research
>> K. Kinugawa,MD PhD, geriatrics, clinical research
>> C. Lafuente, MD PhD, geriatrics, clinical research
>> R. Sherrard, PhD, neurobiology
>> B. Friguet, PhD, aging, stress, proteomics

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Establish an innovative and standardized framework for knowledge discovery, medical intelligence and better standard of care in age-related diseases

> To enable evidence-based standard-of-care and to facilitate translational medicine and translational research

> To enable the identification of **phenotypic and biological markers** that are predictive or indicative of the susceptibility to the pathological consequences of acute/chronic stress in aged patients

> To establish a sustainable framework for future research and care, promote the dissemination of knowledge and enhance the attractiveness of ageing research/gerontology to young doctors and researchers

Secondary objectives are

> To develop statistical models of the clinical features/dynamics of age related main co-morbidities (stress related, or chronic)

> To foster personalized medicine (safety)

> To unravel the molecular determinants/predictors **"disease signatures"** of age related main co-morbidities (stress related, or chronic) – apply to R&D in therapeutics

> To monitor/predict disease burden and socio-economic impact in a **stratified manner**

INNOVATIVE SCIENTIFIC FEATURES

> Standardized expert framework for data collection, analysis and exploitation (several cohorts)

> **Cluster of cohorts:** Design enabling predictive power in the identification of **disease/stress-susceptibility signatures**

> Standardized rater scales and operating procedures

METHODOLOGY QUALITY

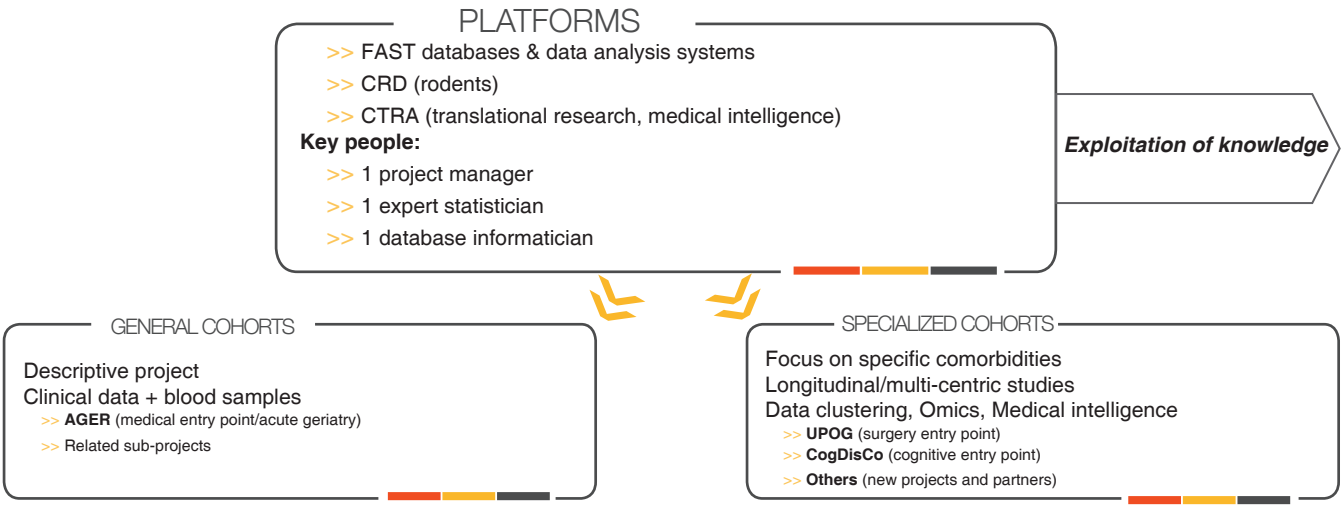
> Knowledge management and reasoning

> Systems/statistical modeling

> Data storage

> Security and quality of biobanking

DESIGN, METHODOLOGY & TIMELINE



UPOG Cohort : patients in perioperative management

Recruitment objectives:	Continuous enrollment
Sites :	Pitié-Salpêtrière hospital, and ongoing collaborations including Saint Antoine, Pompidou and Bichat hospitals (Paris), Grenoble CHU
Inclusion criteria:	> 70 years old with a surgical procedure in the filed of orthopedic surgery admitted in a geriatric peri-operative care unit (UPOG) ; patients characterized with a high one-year mortality (33-50%).

> **Database :** 250 clinical parameters for 706 actual inclusions including demographic data (age 85 ± 6 years old, sex ratio f:m 3:1), 88% orthopedic surgery with 426 hip fractures, with numerous comorbidities (dementia 36%, CHD 19%, hypertension 71%, diabetes 14%, CIRG score 9 ± 4), with numerous complications (delirium 35%, anemia 83%, pressure sores 10%, ACS 9%, infections 26%), and relevant outcomes (LOS 11 ± 9 days, in hospital mortality 3.7%, ICU referral 7%)

CogDisCo Cohort (Cognitive Disturbances Cohort) : patients with neurodegenerative disorders

Recruitment objectives:	From 2010 to 2012
Sites :	Geriatric day hospital (CMRR Paris IdF Sud) at Salpetrière hospital, Paris
Inclusion criteria:	All patients with neuropsychological evaluation for cognitive complain in our unit

> **Database :** Mean MMS 23,2 +/- 4,43; Mean BREF 11,9 +/- 3 (75% between 5-9)
HBP 53%, dyslipidemia27%, Ischemic myocardiop 17%, Diab 16%, Depression 33%, Anxiety 25%, mean CIRS 7,2 +/- 3,99

AGER : patients hospitalized in acute geriatrics

Recruitment objectives:	Continuous enrollment
Sites :	All geriatric acute care units partners of the DHU (n=6) in collaboration with emergency departments, plus acute care geriatric units outside FAST (e.g. Henri Mondor Hospital)
Inclusion criteria:	> 70 years old admitted with a medical condition in one of the acute geriatric care unit

> **Database :** 150 clinical parameters selected by physicians including demographic data (age, sex, social conditions), with attended numerous comorbidities (dementia, cardiovascular, respiratory, neurological and osteo-articular diseases), with numerous complications (delirium, pressure sores, acute coronary syndrome, infections, heart failure..), and relevant outcomes (length of stay, in-hospital mortality, transfer to rehab units, home return)

DATABASE & BIOBANK CONTENTS

FAST Consortium cohorts have recruited patients in perioperative management (UPOG), patients with neurodegenerative disorders (CogDisCo) and patients in acute geriatry (AGER)

Database

> **UPOG**

>> **Demographic:** Date of birth, place of birth, gender, current residence / description

>> **Risk factors profiling**

>> **Clinic and co-morbidities:** Weight, height, medical co-morbities, acute events (including delirium, pain, anemia, infections, acute coronary syndrome, heart failure, pulmonary embolism, stroke), electrocardiography, Doppel-Echocardiography, time to surgery, walking ability after surgery and management, rehabilitation data, time to readmission, time to re hospitalization, dependancy and ability to walk at 6 and 12 months

>> **Biologic:** basic haematological and biochemical information

>> **Treatments :** all drugs treatments including pre hospitalisation drugs, drugs used during hospitalization stay and treatment at the end of the rehabilitation, are available and collectable for specific research.

> **CogDisCo**

>> **Demographic:** Date of birth, place of birth, gender, current residence / description

>> Vascular risk factor

>> **Clinic and co-morbidities:** Weight, height, medical co-morbities, clinical examination with scales, ADL-IADL, NPI, GDS, MMSE and scores of neuropsychological test, data for MRI, SPECT, lumbar puncture

>> **Biologic:** biological tests and diagnosis of cognitive disturbances

>> **Treatments:** all drugs are collected at the inclusion and during the follow up

> **AGER (under construction)**

>> 150 clinical parameters selected by physicians including demographic data (age, sex, social conditions), with attended numerous comorbidities (dementia, cardiovascular, respiratory, neurological and osteo-articular diseases), with numerous complications (delirium, pressure sores, acute coronary syndrome, infections, heart failure..), and relevant outcomes (length of stay, in-hospital mortality, transfer to rehab units, home return).

Biobank

> Biobank originalities rely on its framework and expertise enabling development of medical intelligence (versatility of biological and omics signatures)

> Sampling at the inclusion and during the follow up: Blood, serum, plasma, urin, iPS cells (for selected subsets of patients)

> To date, 90 patients have been sampled for specific research in the UPOG cohort (blood) and 60 patients in the CogDisCo cohort (cerebrospinal fluid)

> Basic clinic analysis (haematology, biochamistry, proteinura), deep sequencing in peripheral and iPS cell samples (DNA, RNA/miRNA), Proteomics (oxy-proteome), possibly metabolomics could be performed based on biobank sampling

> Biobank will be useful for genome sequencing/genotyping (all cohorts); methylomes, proteomes and RNA-seq (specialized cohorts only)

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

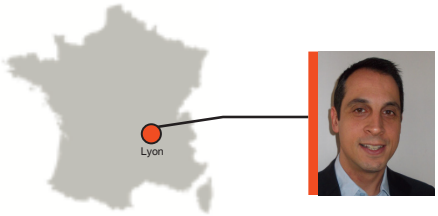
> **Identification of biomarkers** based on the correlation of **clinical, biological, functional and 'omics data**
> Identification of **phenotypic/clinical markers** that may be predictive of elderly disease(s) **progression**
> Identify **'omics signatures** that may correlate with specific **phenotypic patterns** in aging, stress and disease
> Pathophysiology studies for the understanding of disease etiology as guided by rule based **clustering of heterogeneous data** and **detection of stress/disease signatures**
> **Measurement scales** definition and **disease modeling** in the field of **acute care**
> Use **human iPS cells** as a new tool to screen for determinants of genetic susceptibility to stress-related disease in aging
> Explore the **role of adult cell decline** in aging and stress

Clinical development

> **Validation of biomarkers** to define clinical stages and improve therapeutic guidance in aged patients
> **Optimization of clinical studies:** aged patient stratification using standardized scales, collection of gene expression signatures (e.g. measures and scales and sub population characterization)
> **Epidemiological studies** to support market access thanks to statistical modeling
> **Clinical definition and modeling of specific stress/disease scenarios**

Outcomes research

> **Better understanding** of age-related diseases/multi-morbidity and **guidance to clinical trials** (drug repositioning, drug efficacy, identification of target disease)
> Generate **statistical models of clinical evolution** using a medical intelligence approach based on high quality FAST cohorts
> **Pharmaco-epidemiological studies:** drug safety, "real-world" use, effectiveness, practices patterns, acceptance, risk/benefit, risk management.
> **Pharmaco-economic studies** cost/benefit, health economic outcomes
> **Comparative studies** to assess product efficiency across populations
> **Quality of life** studies taking advantage of new knowledge on the individual susceptibility to acute stress and/or chronic conditions



Pr. Stéphane NANCEY,
Head of the Department of Gastroenterology, CHU Lyon-Sud

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OVERVIEW

AT A GLANCE

> Immunology & inflammation
> Crohn Disease
> Crohn patients in remission
> Coordinated by Pr. Stephane Nancey
> Hospices Civils de Lyon Sponsorship
> Cohort labelled and supported by "Lyon Biopôle"

KEY FACTS & FIGURES

> Patient inclusion ongoing
> 150 patients already included
> 250 expected Crohn patients in remission
> One year follow-up
> Blood, serum, plasma, feces, urine biobanking

The goal of FEMTOKINE is to improve therapeutic management of Crohn's patients and eventually limit complications and need for surgery through identification of non-invasive prognostic markers of relapse in remitting Crohn's patients.

Current mainstream biomarker is CRP, but its specificity is modest and there is no consensus on how to best use CRP to guide therapy. Other potentially more interesting biomarkers will be assesssed in Femtokine (lymphocytes subtypes, cytokines...).

An objective of Femtokine is also to identify markers of therapeutic response in the group of patients who relapse.

Currently, there is few dedicated biobank of Crohn's disease available in France: Femtokine will also allow the creation of a comprehensive biobank (serum, plasma, feces, urine) of well phenotyped patients.

Translational Research Clinical Development Outcomes Research

Positioning

> This cohort of Crohn's patients in remission is quite unique. It is very different of other projects in France (EPIMAD is an epidemiologic registry in Northern France and The REMIND cohort considers Crohn patients after surgery).

> FEMTOKINE will be associated with an approved EU project for a biobank dedicated to inflammatory bowel diseases.

> Industrial partnership have already been established around FEMTOKINE.

LEADERSHIP

FEMTOKINE leadership team is made up of Pr. S. Nancey and B. Flourié, two recognized international experts in the field of Crohn Disease and of Pr. J. Bienvenu, Head of the lab of Immunology , Pr. R. Ecochard, Head of Biostatistics at Hospices Civils de Lyon and Dr. D. Kaiserlian, Head of the labteam at the International Centre for Research in Infectiology (CIRI)

Stéphane Nancey, MD, Ph.D.

- Pr. of Gastoenterology
- Dr. in Immunology, University Cl. Bernard Lyon 1
- Head of the Department of Gastroenterology, CHU Lyon-Sud
- Research Fellow Harvard Medical School (Pr. Blumberg) 2007-2008
- Head of the research group on immunopathology of IBD at INSERM U1111 (CIRI)

Jacques Bienvenu, Ph.D.

- Head of the laboratory of Immunology, CHU Lyon-Sud

René Ecochard, MD, Ph.D.

- Pr. of Biostatistics, Head of the Department, CHU Lyon-Sud

Bernard Flourie, MD, Ph.D.

- Pr. of Gastoenterology, University Cl. Bernard Lyon 1
- Member of the team n°9 in INSERM U1111 (CIRI)
- Member of the Scientific Committee of GETAID

Dominique Kaiserlian, MD, Ph.D.

- Head of the team N°9-CIRI "Mucosal immunology-Vaccination-Biotherapy"

SCIENTIFIC NETWORK & MANAGEMENT

FEMTOKINE cohort in network with an international consortium with:

Academic partners:

> Hospices Civils de Lyon, CHU Lyon, France
>> Laboratory of Immunology (Pr. J. Bienvenu)
>> Department of Gastroenterology (Pr. S. Nancey)
>> Department of Biostatistics (Pr. R. Ecochard)

> Hôpital Nord, CHU Saint Etienne, France
>> Department of Gastroenterology (Pr. X. Roblin)

> Hôpital Gabriel-Montpied, CHU Clermont-Ferrand, France
>> Department of Gastroenterology (Pr. G. Bommelaer)

Industrial partners, including:

>> Indicia, Lyon, France, which is a service provider specialized in the evaluation of the immunogenicity of therapeutic proteins and the study of the immune response by measuring cytokines and biomarkers expression

>> TxCell, Nice, France, which develops innovative, personalized cell-based immunotherapies using antigen specific regulatory T-cells (Ag-Tregs) for severe chronic inflammatory and autoimmune diseases

>> Singulex, San Diego, USA, which is the developer and leading provider of single molecule counting (SMCTM) technology for clinical diagnostics and scientific discovery

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Main objective of FEMTOKINE is to identify non-invasive markers predictive of relapse in remitting Crohn's patients, in order to improve therapeutic management of these patients and possibly prevent surgery (personalized, pre-emptive medicine)

Secondary objectives:

> Set-up of a comprehensive biobank of Crohn's patients, well phenotyped (disease location, behaviour, concomitant therapies…)

> Identification of biomarkers predictive of treatment response in patients relapsing

> Explore the influence of patients Quality of Life and stress on inflammatory biomarkers

INNOVATIVE SCIENTIFIC FEATURES

> Femtokine is unique as a cohort of CD patients in **clinical remission**

> This is a carefully characterized cohort of patients with extensive and repeated collection of biological material

> Extensive workup of patients every 3 months

> Highly sensitive methods (for proteomics Erenna assay is one log more sensitive than ELISA)

METHODOLOGY QUALITY

> High level of data monitoring with dedicated CRA and random scheme for Source Data Verification

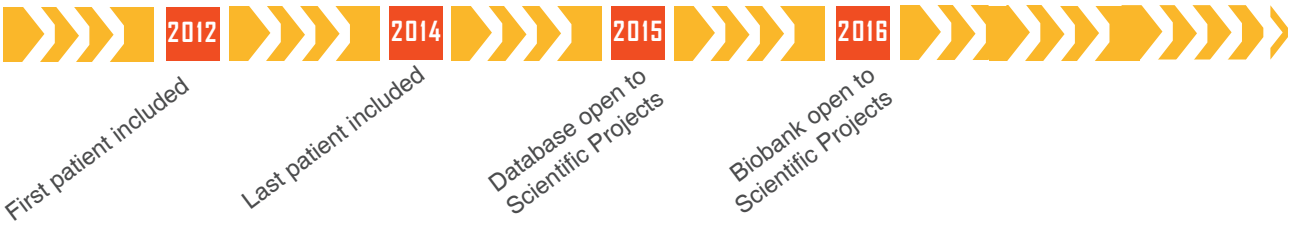
> Data-Management by Hospices Civils de Lyon

> 100% of patients files reviewed by Study Coordinating Centre

> Full collection of treatments and medical events during study follow-up

> State-of-the-Art Biobank procedures, certified according to the SOPs of Hospices Civils de Lyon TUMOROTEK®

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives: Enrollement has started in 2012. Today 150 patients are enrolled (the target number is 250 and should be reached during 2014)

Sites: This is a carefuly selected, well characterized series of patients from 3 hospitals centres. Only about 10% of Crohn patients seen in the clinic are eligible to enroll into the cohort

Inclusion criteria: All patients seen in the clinic who are in clinical remission and
> Without steroid treatment for the last three months
> With stable therapy for at least the last six months
> Patient with healthcare insurance

Exclusion criteria:
> Patients who could not be followed (e.g., multiple surgeries, stoma)>
> Harley-Bradshaw score ≥5
> Perineal fistula

INCLUSION COLLECTION
Database: Demographic, clinical evaluation, signs and symptoms, Harvey-Bradshaw index, CDAI* score, prior and concomitant therapies, history of the disease, QoL data, stress and coping scales, biological data, immunophenotype
Biobank: Serum, plasma, stool supernatants samples

FOLLOW-UP : 4 TIMES PER YEAR
Database: Visit every 3 months with complete data collection, careful study monitoring with dedicated CRAs, source Data verification with random sampling procedures
Biobank: Biological collection (serum, plasma, feces, urine) according to Lyon TUMOROTEK SOPs (certified Biobank)

**CDAI : Crohn's Disease Activity Index*

DATABASE & BIOBANK CONTENTS

Database

>> Demographic, clinical evaluation, signs and symptoms, Harvey-Bradshaw index, CDAI score, prior and concomitant therapies, history of the disease, QoL data, stress and coping scales, biological data, immunophenotype

>> Cross imaging findings (Entero-MRI, US) and endoscopy were not systematic and let at the discretion of the physician

Biobank

>> Serum, plasma, stool supernatants sampling

>> Measurements of immunologic and inflammatory parameters, surface and intracelular cell markers, lymphocyte subsets, cytokines, chemokines, calprotectin S100A12, neopterin, lactoferrin, M2PK...

>> 162 patients who have been sampled, 8046 samples and approximately 50 samples per patient

>> Analysis of the serum and stool samples by ELISA, Erenna and cell suspensions by flow cytometry

>> Strict conditions of transport and storage of the samples in the Biobank

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>> Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab is associated with a profound long-lasting depletion of Foxp3+ regulatory T cells: a mechanistic explanation for ipilimumab-induced severe enterocolitis? Nancey S, Boschetti G, Cotte E, Ruel K, Almeras T, Chauvenet M, Stroeymeyt K, Moussata D, Kaiserlian D, Flourié B. Inflamm Bowel Dis. 2012 Aug;18(8):E1598-600.

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>> Therapy with anti-TNF antibody enhances number and function of Foxp3(+) regulatory T cells in inflammatory bowel diseases. Boschetti G, Nancey S, Sardi F, Roblin X, Flourié B, Kaiserlian D. Inflamm Bowel Dis. 2011 Jan;17(1):160-70

RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Identification of emerging biomarkers** for the development of diagnostic or prognostic tests based on the correlation of biological and clinical data
>> Immunologic markers
>> Inflammatory markers

> **Pathophysiology studies** for a better mechanistic understanding of disease
>> Identification of biomarkers predictive of treatment response in patients relapsing

> Development and validation **of novel index combining most accurate biomarkers capable to predict the risk of relapse of CD and identify patients at high risk of further flares**

> **Quality of life studies**
>> Correlation between variation of biomarkers and stress and quality of life scores (Hassles, coping, SLC-90R, PSS10, IBDQ, ENRICHD and Paykel list)
>> Identification of patients profile

> Biobank of Crohn's patients according to Lyon TUMOROTEK SOPs (certified Biobank)
>> Serum
>> Plasma
>> Stools

Public-Private partnership interest:
Companies involved in pharmaceutical and diagnostic and medical devices would be interested by the cohort for validating novel and reliable biomarkers useful to predict active/inactive disease, response to therapy…

FREGAT :
FRENCH ESOGASTRIC TUMORS DATA BASE

aviesan
ITMO Santé publique

FREGAT
Base de Données Nationale
Des Cancers Oeso-Gastriques

Pr. Christophe MARIETTE
Professor of Surgery, Head of the Surgiical and Clinical Research department, CHRU Lille

Pr. Antoine ADENIS
Professor of Medical Oncology, Deputy Director, Centre Oscar Lambret, Lille

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OVERVIEW

AT A GLANCE

> Oncology
> Oesophago-gastric cancers
> Coordinated by Pr .C. MARIETTE
> CHRU Lille Sponsorship
> Funded by INCa

KEY FACTS & FIGURES

> Status: Inclusion will start in mid 2014
> 15 000 enrolled patients
> At least 3 years follow-up
> National multicentre cohort
> Tumour and serum biobanks

The challenge of FREGAT is to investigate, in an initial phase, causes of treatment resistance observed in oeso-gastric tumours.

FREGAT is a prospective clinico-biological database dedicated to oesophago-gastric cancers that unites the vast majority of clinical teams and University hospital centres who struggle against these cancers and care for the majority of cases nationally, based on many existing networks that ensure its implementation and its quality.

A personalized approach to oesophago-gastric cancers is emerging and requires a rapid and multi-disciplinary development. The care of oesophago-gastric cancers is complex and resistance to loco-regional and systemic treatments is frequent, meaning new clinical and epidemiological studies, relying on biological and tumoral collection, must be put in place in a grand scale.

Translational Research Clinical Development Outcomes Research

2014 — First patient included
2015 — Data first availability
2017 — Last patient included execpt if prolonged

Positioning

> To date, there is no similar project worldwide collecting so widely clinical, biological and tumor data. FREGAT Database aims to be opened to scientific community at European and International levels for academic as well as industrial researchers.

> FREGAT is closely working with Biobanques Infrastructure and F-CRIN. In a second time, inclusion will be extended in Europe. Letter of intention have already been signed by European research teams.

> Partnerships with pharmaceutical and diagnostic companies are already ongoing.

LEADERSHIP

Christophe Mariette, MD, Ph.D., Professor of Surgery, Head of the Surgical and Clinical Research department, CHRU Lille

Well-known international expert in the field of the medical and surgical approaches in oesophageal and gastric cancers

Main investigator or involved in clinical trials from basic and translational research programs

Network
- >> National coordinator of the French oeso-gastric surgical working group
- >> Scientific Director proogram "Tumor resistance" SIRIC OncoLille Labelled by the INCa (excellence centre in oncology)
- >> Scientific President of the French Society of Digestive Surgery (SFCD)
- >> President of the French Federation of Surgical Research (FRENCH)
- >> Member of the Clinical Research Committee of The National Cancer Institute (INCa)
- >> Tresurer of the European Society for Diseases of the Esophagus (ESDE)

Editorial board and reviewing
- >> Editorial board member of the European Journal of Surgical Oncology (EJSO)
- >> International reviewer for clinical trial grants dealing with oeso-gastric pathologies for the Health Ministries of Germany, Ireland, UK, Netherlands, Switzerland, Canada…
- >> Reviewer for notably The Lancet and The Lancet Oncology

Current collaborations
- >> EORTC and PRODIGE oncological groups
- >> Many Europeans investigators and scientific societies
- >> Different industrial sponsorships

Antoine Adenis, MD, Ph.D., Professor of Medical Oncology, Deputy Director, Centre Oscar Lambret

Expert in multidisciplinary gastrointestinal oncology

Principal investigator or co Investigator in clinical trials

Network
- >> Public Health expertise at the ANSM
- >> Member of Consensus Groups, on behalf the «Haute Autorité de Santé» (HAS), in charge of producing national recommendations on colon and rectal cancer and liver metastases treatment
- >> President Unicancer GI and PRODIGE groups

Editorial board and reviewing
- >> Reviewer for Br J Cancer, Eur J Cancer
- >> Reviewer for clinical trial grants dealing with GI oncology

Collaborations
- >> EORTC, PRODIGE and UNIcancer GI oncological groups
- >> EORTC and French Sarcoma Groups
- >> Seoul University (Korea) Pr. J Lee, Samsung Medical Centre
- >> Different industrial sponsorships

SCIENTIFIC NETWORK & MANAGEMENT

Pr. C. Mariette is closely working with European centres of excellence in oeso-gastric cancers (OGC) and already engaged in a process for a European Database construction dedicated to OGC. These initiative is leading by William Allum from the Royal Marsden NHS Foundation Trust in collaboration with:

- >> R. Hardwick (UK)
- >> G. De Manzoni (IT)
- >> F. Roviello (IT)
- >> D. Dugo (IT)
- >> A. Garofalo (IT)
- >> M. DeGiuli (IT)
- >> J. Kulig (POL)
- >> HJ Meyer (DE)
- >> A. Hoelscher (DE)
- >> J. Johansson (SE)
- >> T. Zilling (SE)
- >> L. Jensen (DK)
- >> S. Gonzalez (ES)
- >> J. Reynolds (IRE)
- >> C. Van De Velde (NL)
- >> P. Naredi (SE)
- >> C. Van Den Broek (NL)
- >> J. Dikken (NL)

Through its Scientific Advisory Board, FREGAT implicates experts in:

- >> OGC: Well-recognized experts in the field of oesophago-gastric cancers
- >> Epidemiology: Michel Henry-Amar, Pr. G. Launois,
- >> Tumour Bioanking: Pr. MC. Copin, Pr. MD. Diébold
- >> Biostatistic: Pr. A. Duhamel, Pr. A. Kramar
- >> Human and social sciences: Pr V. Christophe
- >> Quality of life: Dr F. Bonnetain
- >> Ethical and legal issues: P. Guyon

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

The main scientific questions that can be addressed are

> Identification of **new prognostic** and **predictive** factors

> Validation of promising predictive **markers to anti-tumoral therapy**

> Understanding of underlying **mechanisms** and **new drugs development**

> **Impact evaluation** of current treatment strategies

> Identification of **epidemiological** and **socioeconomic determinants** which barrier access to health care system and medical treatments starting

> Better understanding **therapeutic strategies efficiency** and their impact on the patients' survival and quality of life

INNOVATIVE SCIENTIFIC FEATURES

> First and the largest dedicated OG clinico-biological data

> Human and social sciences data

> National Network

> Built to be extended to European Partners

> Based on a network that has already produced high level scientific paper

METHODOLOGY QUALITY

> All data will be transmitted from the interface to the database in a secure channel through a protocol such as SSL. The clinical database will be stored in the North-West cancéropôle DTC labelled by the INCa

> Data monitoring and monitoring of the quality of preserved tissues will be performed every six months

> Site audit every year for quality

> All Fregat's procedures are in compliance with national and international guidelines

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives: 15 000 newly diagnosed OGC patient

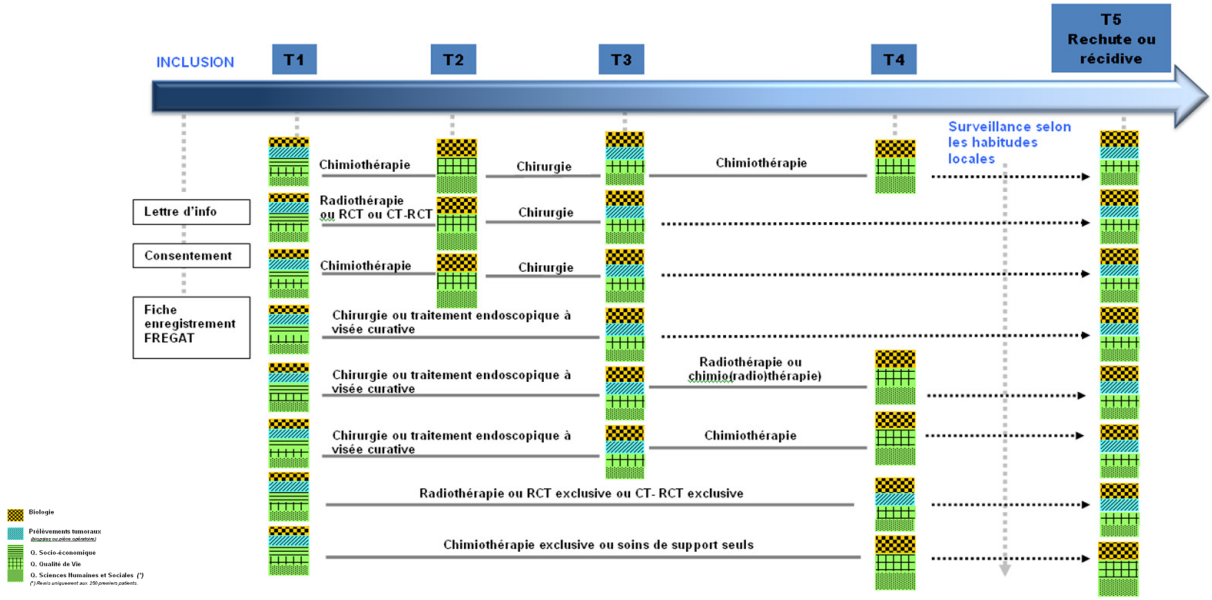
Sites: 33 centres with 46 clinical teams

Inclusion criteria:
> Patient with oesophageal carcinoma, of oesogastric junction or gastric newly diagnosed by biopsy, irrespective of histological type, tumoral stage, first physician seen or the therapeutic strategy
> Patient (men or women) ≥ 18 years old
> Treatment-Naive Patients
> Patient healthcare insurance

Exclusion criteria:
> Patient < 18 years old
> Patient under administrative supervision
> Not french-speaking patients
> Patients refusal or without sign consent

INCLUSION COLLECTION
Database: Prospective collection of clinical, epidemiological, behavioral and social data, histological diagnostic
Biobank: Biological samples (3 tubes : dried tube, EDTA and heparin tubes), Tumoral samples (10 pre-therapeutic biopsy)

FOLLOW-UP : ONCE A YEAR
Database: Collection of clinical data, therapeutic strategies, severe toxicity (grade 3-4), behavioral, social and quality of life data
Biobank: Biological samples before and after treatments and at recurrence (3 tubes : dried tube, EDTA and heparin tubes), Tumoral samples (biopsy and/or operative specimen)



DATABASE & BIOBANK CONTENTS

Database

>> **Demographic:** Date of birth, place of birth, gender, current residence / description, distance to the physician, distance to the healthcare centre, transport, environmental factors, previous history of cancer

>> **Risk factors linked to OGC:** Alcohol and tobacco consumption, reflux, obesity, dietary habits

>> **Clinic:** Weight, height, medical co-morbities, past history of other cancer, date of first symptom/ description, date of first consultation, type of clinician consulted, symptoms, current medications for other diseases, nutritional parameters

>> **Biologic:** Collections of variables related to inflammation, nutrition

>> **Therapeutic:** medical, surgical, radiotherapeutic, palliative strategies with evaluation of response and tolerance

>> **Psycho-socio-economic variable:** family circle, isolation, education, job at inclusion, coping and other psychological factors evaluated with a specific questionnaire

>> **Quality of life:** EORTC QLQ-C30 general questionnaire and EORTC QLQ-OG25 specific module

>> **Date and cause of death, date of last follow-up**

Biobank

>> **Tumour/Pathology:** Pre-therapeutic biopsies, Post-therapeutic biopsies and Tumor banking, location, pTNM stage, usual pathological variables, Observation of resistance to treatment markers, Metastasis, Regression, Progression, Recurrence, Histology, Effect of neo-adjuvant treatment

>> **Blood samples:** only in high volume voluntary centres with a labeled BRC (estimated to be n=5): in those centres engaged in the serum banking process all required samples will be collected for each patient included in the database

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Translational research

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Clinical development

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Outcomes research

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> Identify and validate underlying **molecular mechanisms** responsible for **tumour response** and/or long term survival in order to discover and develop **new targeted therapies**

> Evaluating **tumour molecular characteristics variations** before and after neoadjuvant chemo(radiation) in OGC

> Identification of **predictive factors** for response to neaodjuvant treatment through **correlation of molecular data** (pretherapeutic biopsies) and **clinical data** with histopathological response in patients undergoing surgical resection for an OGC after neoadjuvant treatment

Clinical development

> Identify **key factors** and **key molecular determinants** linked to tumoural response/resistance to treatment, which will allow to design dedicated trials for sub-groups of patients and provide a **personalized therapeutic approach**

> Better understanding OGC evolution by analyzing **epidemiological variations** across time periods and region

> **Validation** of **promising molecular markers** recently identified

Outcomes research

> Better characterization environmental and **behavioural risks**

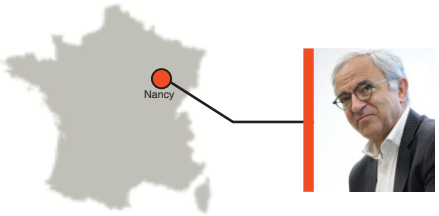
> Analyze **socio-geographic OGC disparities** and reduce health and social inequalities in French OGC patients

> Evaluate the **impact** of the various **therapeutic strategies** used in OGC patients and eventually in different at risk subgroups (older patients, histological subtypes, tumoral stage)

> Provide data to health authorities regarding **OGC surgical and medical practice** in France for further socio-economic health decision making

> Improve access to care and to treatment in this high risk population

> Increase knowledge of **HRQL in OGC** subgroups of patients (old patients, high comorbidity patients)



Pr. Faiez ZANNAD
MD, Ph.D., Professor of Therapeutic- Cardiology, Head of Hypertension and Heart Failure Inserm team
Coordinator of EU FP7 HOMAGE

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OVERVIEW

AT A GLANCE

> Cardiology
> Heart Failure and associated co-morbidities
> CV risk patients
> Coordinated by Pr. F.Zannad
> Inserm coordination
> Funded by EU FP7 & ANR

KEY FACTS & FIGURES

> Status: Data banking achieved and Bio banking in progress
> Currently: 43 133 subjects
>> 7 124 healthy individuals
>> 4 260 HF
>> 5 829 individuals with CV risk factors
>> 26 490 patients from randomized control trials (HF, hypertension, high cardiovascular risk)
> Up to 25 years follow-up data yet available in 38144 individuals
> Multicentric international cohort integrating 20 cohorts
> Urine, Blood samples, DNA, Cardio biopsy biobanking

HOMAGE project aims to lay the ground for future incorporation of Biomarkers in diagnostic guidelines and routine clinical practice to assist physicians in predicting patients at risk of developing Heart failure and therapeutic decision making based on biomarker mechanistic stratification (personalized medicine). HOMAGE could also allow mechanistic phenotyping based on biomarker profiling of patients at risk of Heart Failure and:

>> HOMAGE originality relies on a retrospective and prospective long-term longitudinal follow-up of multiple ethnicities subjects around the world.

>> Over 60 000 samples of blood, serum, plasma, DNA and urine have been collected from more than 40 000 subjects.

>> HOMAGE represents around 120 000 person-years of follow-up with 2 500 incident cases of Heart Failure.

Translational Research Clinical Development Outcomes Research

Positioning

> HOMAGE is a consortium of academic and SME's partners based on European projects FP7 n° 305507 taking advantage of the implication of several HOMAGE partners in other epidemiologic projects.

> HOMAGE cohort is the merge of 20 European, North American and Asian cohorts.

> Unique, thanks to its focus on heart failure risk and co-morbidities long follow-up and size.

LEADERSHIP

Pr. Faiez Zannad
MD, Ph.D., Professor of Therapeutics, Head of the Division of Heart Failure, Hypertension and Preventive Cardiology/ dept of Cardiovascular Disease, CHU Nancy, Director of the Clinical Investigation Center of Nancy

Renowned international expert in the area of physiopathology and pharmacotherapeutics of hypertension and HF.

Renowned for his significant contributions in the area of mineralocorticoid receptor blocker therapy in HF

Principal Investigator and/or chair in a number of major cardiovascular clinical trials, basic and translational research programs

Network

>> National coordinator of the network of 15 cardiovascular CIC in France

>> Past Chairman of the Board of the French Society of Hypertension

>> Fellow of the European Society of Cardiology (ESC)

>> Past-Chairman of the ESC Working group on pharmacology and drug therapy

>> Board member of the ESC Heart Failure Association

>> Contribution to clinical trial science and methodology in CV disease, through various publications and the organisation of CardioVascular Clinical Trialists meetings (www.globalcvctforum.com)

Editorial board and reviewing

>> Past Co- Editor in chief of Fundamental and Clinical Pharmacology (2005-2010), the official journal of the European Federation of Pharmacological Societies (EPHAR)

>> Member of the Editorial boards of a number of journals in the field of Cardiology, Hypertension and Cardiovascular Pharmacology

Current collaborations

>> Member of several Steering Committees, Critical Event Committees and Data Safety and Monitoring Boards of many major CV trials

>> Coordinating a Joint Research Program on transition from Hypertension to Heart Failure, in the 6th FP EU funded Network Excellence "InGeniousHyperCare" and of Workpackages in two 7th FP grants (BIOSTAT and MEDIA) , 2010-14: EU 7th FP, EU 7th FP Heart failure OMics and AGEing (HOMAGE), General Coordinator, EU 7th FP FIBRosis as a TARGET in Heart Failure (FIBROTARGETS), General coordinator

Publications (As per December 1st 2013)

>> PubMed: 423 publications

>> Google Scholar: 33 824 Citations, h-Index = 63

SCIENTIFIC NETWORK & MANAGEMENT

Collaboration network with European and International cohorts

>> The project is linked with other cohorts: PRIORITY Trial (Gentofte, Denmark), The Framingham Heart Study (Boston, USA), Health ABC (Atlanta, USA), Asian Cohorts (Singapore and New Zealand), Lucky cohorts (Luxembourg)

>> HOMAGE is a 6-year European Research network supported by the EU under the FP7

HOMAGE is based on network of key opinion leaders and international experts with high transdisciplinary expertise:

>> **Basic research:** F. Pinet, P. Rouet, S. Masson, A. Gonzalez-Amiqueo, B. Schroen

>> **Translational research:** T. Thum, S. Heymans ,P. Rossignol, B. Pieske, J. Diez, A. Mebazaa

>> **Clinical trial:** JGF Cleland, L. Neyses, K. McDonald, R. Latini, J. Staessen, S. Pocock, J. Butler, D. Levy, J. Ho, C. Delles, H-P. Brunner-La-Rocca, EDDH (academic CRO)

>> **SMEs:** MOSAIQUE DIAGNOSTICS, ACS BIOMARKER, RANDOX TESTING SERVICE, Inserm Transfert

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

> Validate the association of “omics”-based biomarkers with risk of developing heart failure and co-morbid conditions in cross-sectional at risk and population cohort

> Demonstrate the incremental value of omics based biomarkers, alone or integrated with established clinical phenotypes and classical biomarkers over the existing predictive models

INNOVATIVE SCIENTIFIC FEATURES

> Well characterized cohorts
> Multiple ethnicities and geographies
> Long term follow-up
> Adjudicated Mortality and Morbidity outcomes

METHODOLOGY QUALITY

> Single integrative database
> Modern bio-banking.
> State of art management tools (ATOS, SOPs, ...)
> Security and quality procedures
> Certification

DESIGN, METHODOLOGY & TIMELINE

INTEGRATED HOMAGE COHORT

POPULATION COHORTS	STANISLAS	FLEMENGHO	PREDICTOR
Number of patients	4295	828	2001
Women, no (%)	2138 (49.8)	421 (50.9)	967 (48.3)
Age, years	27.0±14.3	51.2±15.6	73.4±5.0

HEART FAILURE PATIENTS	HFGR	LEITZARAN	HULL LIFELAB
Number of patients	218	233	3239
Women, no (%)	59 (27.1)	109 (46.8)	1068 (33.0)
Age, years	67.1±12.5	74.3±9.3	70.7±11.0

CV-RISK PATIENTS	ADELAHYDE	R2C2	BIOMARCOEURS	IBLOMAVED	REVE	GECOH	HVC	DYDA
Number of patients	378	169	1117	570	512	266	1880	937
Women, no (%)	205 (54.2)	87 (51.5)	473 (42.3)	174 (30.5)	113 (22.1)	162 (60.9)	961 (51.1)	358 (38.2)
Age, years	70.4±6.3	54.8±5.8	70.7±16.0	60.2±12.7	57.6±13.8	49.8±15.6	57.7±15.0	61.9±7.6

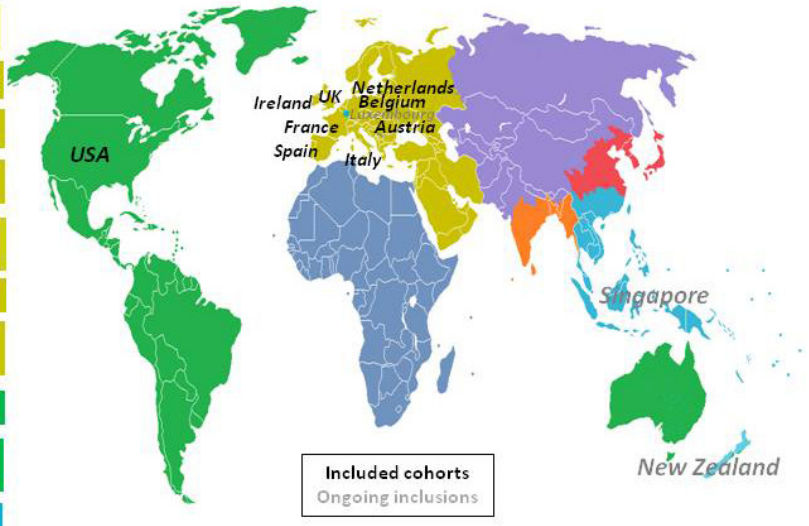
RANDOMIZED CTs	EPATH	STYRIAN VITD	STOP-HF	TIME-CHF	ASCOT	PROSPER
Number of patients	40	286	481	622	19257	5804
Women, no (%)	32 (80.0)	136 (47.6)	264 (54.9)	253 (40.7)	4515 (23.5)	3000 (51.7)
Age, years	68.7±10.0	60.4±10.6	67.1±9.8	76.9±7.6	63.0±8.5	75.3±3.3

HOMAGE WORLD-WILDE collection of data

Pr F. Zannad

- Pr A. Mebazaa *France*
- Pr B. Pieske *Austria*
- Pr J. Diez *Spain*
- Pr K. McDonald *Ireland*
- Pr JGF. Cleland *UK*
- Pr S. Pocock *UK*
- Pr S. Heymans *Netherland*
- Pr R. Latini *Italy*
- Pr JA. Staessen *Belgium*
- Pr J. Butler *USA*
- Prs D. Levy and J. Ho *USA*
- Pr C. Lam *Singapore*
- Pr M. Richards *New Zealand*
- Pr D. Wagner *Luxembourg*

As the leader of the HOMAGE consortium, Prof F. Zannad has assembled and integrated a network of clinicians with internationally recognized expertise and experience in Heart Failure.



- Unique data collection (over 40,000 individuals)
- Multiple ethnical groups

DATABASE & BIOBANK CONTENTS

Database

> Baseline data (yet all 20 integrated cohorts): Identification of the individual, Anthropometrics, Lifestyle information, Medical history, Medication

> Collected data

- >> Blood pressure
- >> Arterial properties
- >> Biochemistry/haematology blood
- >> ECG
- >> Echocardiography
- >> Echocardiography Doppler
- >> Urine
- >> NYHA class
- >> Outcome/events

> Follow-up data: from 1 to 25 years, Incidence on morbidity and mortality

Biobank

> Nature of the biofluids: Blood, Whole blood, Serum, Plasma, PBMC, Urine

> Maximal Capacity: ~43 000 patients with an average 2 samples at 2 time points per patient with expected over 160 000 samples

> Standard operating procedures (SOPs) for Biobanking:

- >> Queries on sample: type, collection, processing, volume, quantity
- >> Central biobank: aliquoting, bar code labelling
- >> Transport: standardized by using a single Shipping company
- >> Storage: -80°C

> Integration into an ATOS database

BIBLIOGRAPHY

Translational research

Publications:

>> Díez J.Association of cardiotrophin-1 with myocardial fibrosis in hypertensive patients with heart failure.Hypertension. 2014 Mar;63(3):483-9

>> Heymans S: Absence of trhombospondin-2 causes aged-related dilated cardiomyopathy Circulation 2009, 120:1585-1597

Patents:

>> PCT/EP2010/056931: POST-TRANSLATION MODIFIED CARDIAC TROPONIN T AS A BIOMARKER OF A RISK FOR HEART FAILURE

>> PCT/ES2005/000227: USE OF A C-TERMINAL FRAGMENT OF CARDIOTROPHIN-1 AS A CARDIOTROPHIN-1 MARKER

>> PCT/EP2004/010879: METHOD FOR IDENTIFYING A SUBJECT AT RISK OF DEVELOPING HEART FAILURE BY DETERMINING THE LEVEL OF GALECTIN-3 OR THROMBOSPONDIN-2

Outcomes research

Publications:

>> Thum T. : Gene expression in distinct regions of the heart, Lancet 2000, 355:979-83;

>> Brunner-La Rocca HP : Safety and tolerability of intensified, N-terminal pro brain natriuretic peptide-guided compared with standard medical therapy in elderly patients with congestive heart failure: results from TIME-CHF. Eur J Heart Fail. 2013 Aug;15(8):910-8

Patents:

>> PCT/ES2008/000620: USE OF TRUNCATED PPAR-ALPHA INHIBITORS IN THE TREATMENT OF HEART FAILURE IN PATIENTS WITH HYPERTENSIVE CARDIOPATHY

>> US2008/0193954A1: METHOD FOR DIAGNOSING A SUBJECT AT RISK OF DEVELOPING HEART FAILURE

Outcomes research

Publications:

>> Zannad F.: The EMPHASIS-HF Study group. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms N Engl J Med 2011,364:11-21

>> Cleland JGF: The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. Lancet. 2011 378(9792):676-83

Patents:

>> EP10306338 5:DIAGNOSTIC AND TREATMENT OF CRHONIC HEART FAILURE

>> PCT/EP2011/051088: BIOMARKERS OF CARDIOVASCULAR DISEASE INCLUDING LRG

RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Identification of biomarkers detected by «omic» technologies (unbiaised approaches)** for the development of diagnostic or prognostic tests based on the correlation of biological and clinical data

> **Pathophysiology studies** for the understanding of HF disease development (etiology)

> **Development and validation** of novel measurement scales and disease models

Clinical development

> **Validation of biomarkers** to refine clinical stages and improve therapeutic guidance

> **Optimization of clinical studies** (timing, measures and scales, sub population characterization, design….)

> **Support clinical enrollment : HOMAGE prospective interventional study** will investigate an innovative «omics BM-guided» therapy to HF that will focus on ECM remodelling/inflammation as one of the potential mechanism for the development of HF. Enrollment of 800 additional patients out of 5 000 newly screened individuals

> **Epidemiological studies** to support market access

Outcomes research

> **Pharmaco-epidemiological studies:** Risk/benefit, risk management, personalized HF treatment

> **Pharmaco-economic studies** cost/benefit

> **Comparative studies** to assess the role of the BM in prevention, segmentation, treatment and management of HF

> **Quality of life studies** by increasing the number of healthy life years

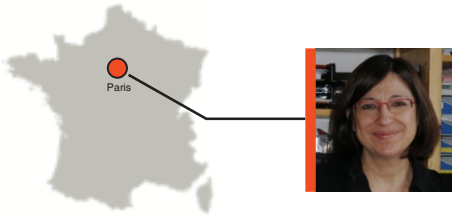
Public-Private partnership interest:

> Providing unprecedented access to amongst the largest patient cohorts in the world
> Fostering their interaction with leading clinicians in the field
> Engaging the power of leading experts in biomedical statistics and bioinformatics
> Enabling companies to select the BM or BM combination and prepare development plan
> Appreciate performance of multimarkers assays
> Provision of some or all the samples needed in the development of the market-ready commercial product

HOPE-EPI :
EPIDEMIOLOGICAL RESEARCH IN PEDIATRIC HEMATO-ONCOLOGY-EPIDEMIOLOGY

aviesan
ITMO Santé publique

hope-epi
plateforme épidémiologique en hémato-oncologie pédiatrique



Jacqueline CLAVEL
MD, Ph.D., Research Director at Inserm, Head of Environmental Epidemiology of Cancers team, Villejuif

Jacqueline.clavel@inserm.fr

OVERVIEW

AT A GLANCE

> Oncology
> Childhood cancers
> Children <18 years with any cancer
> Coordinated by Jacqueline Clavel
> Université Paris Sud Sponsorship
> Funded by ANR and INCA

KEY FACTS & FIGURES

> Inclusions and follow-up ongoing
> 22 000 registry cases
> Cohorts of survivors: 1946-1999 n=18 000 2000- 2013 n=22 000
> Over 10 years follow-up
> Multicentric cohort with 40 centers
> Virtual biobanking (tumors and constitutional) with 1 500 cases
> Medico administrative database linkage with SNIIRAM

HOPE-EPI is a national research infrastructure on childhood cancers constituted by several components:

> French National Registry of Childhood Cancers (RNCE): an exhaustive national recording of pediatric cancer cases (all cancers <18 years)
> French national virtual biobank for childhood cancers (BIOCAP)
> French Childhood Cancer Survivor Study (F3C) including
>> FCCSS cohort of solid tumors, 1946-1999
>> LEA cohort of childhood hematopoietic malignancies, since 1980
>> COHOPER systematic national follow-up of childhood cancer cases (<18 years) based since 2000
> Database of doses of radiotherapy (PEDIART)

Pooling the work to collect data and validate information and health events targeting

> Environmental and genetic risk factors
> Disparities in childhood cancers management and social and territorial determinants
> Outcomes and iatrogenic effects of treatments
> Short, intermediate and long-term state of health and determinants of their quality of life

Translational Research Clinical Development Outcomes Research

Positioning

> Collaboration with ENCCA (European Network for Cancer Research in Children and Adolescents) work package on the contribution of registries to clinical research in pediatric oncology.
> Collaboration with European survivor cohorts PANCARE (Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer) and PanCareSurFup (Survivor and Follow-up studies).

LEADERSHIP

HOPE-EPI's leadership team is set up with a tandem of the renown epidemiologists, J. CLAVEL, F. de VATHAIRE, P. AUQUIER, and the representative of the National Network of Pediatric Oncologists (SFCE)

J. CLAVEL, MD, Ph.D., Research Director Inserm, heads the team of Environmental Epidemiology of Cancers, Inserm U1018, U Paris-Sud (Villejuif)

- Creation and direction, with Brigitte Lacour, of the National Registry of Childhood Cancers
- Extensive experience in the set-up and management of complex national studies
- Creation and direction of the program of research on environmental and genetic risk factors of childhood cancer (national case-control studies, interviews and constitutional DNA bank)
- Close collaboration with the SFCE scientific board since 2004
- 50 articles on childhood cancer in international journals over the last 10 years

P. AUQUIER, MD, Ph.D., Pr. in Epidemiology , Healthcare Economics and Prevention, heads the Public Health and Medical Information Department, CHU Nord (Marseille)

- Co-coordination of LEA cohort of Childhood Hematopoietic Malignancies since 1980
- Coordination of over 40 projects on quality of life (100 referenced articles on the same topic), co-director of the emergent team IRESP-Inserm-DGS Quality of Life and Chronic Diseases

F. de VATHAIRE, Ph.D., Research Director Inserm, heads the team of Radiocarcinogenesis and Iatrogenic Effects of Treatment, Inserm U1018 U Paris-Sud (Villejuif)

- Coordination of the cohort of solid Tumors 1946-1999 (FCCSS)
- Creation a radiotherapy dosimetry team which has set up several programs for the evaluation of the radiation doses received by various organs
- Extensive experience in cohorts in national and international contexts
- Coordination of two European projects addressing constitution of international cohorts
- 30 articles on the fate of childhood cancers survivors over the last 10 years

G. MICHEL, Pr. in Pediatrics, head the Pediatric Hematology and Oncology Dpt, Timone (Marseille)

- Co-coordination of LEA cohort of Childhood Hematopoietic Malignancies since 1980
- Coordination of the inter-regional organization for recourse in pediatric oncology, Chairs the SFCE Hematopoietic Stem Cell Transplant committee

SCIENTIFIC NETWORK & MANAGEMENT

Collaboration network with European or International cohorts:

>> French network of pediatric oncology SFCE (the national network of pediatric oncologists): HOPE-EPI is being developed under the auspices of the SFCE in the work of the childhood cancer epidemiology

>> Research network with ENCCA (European Network for Cancer Research in Children and Adolescents) (FP7) project of observational clinical research based on registries

>> Collaboration with European registries ACCIS (Automated Childhood Cancer Information System), ENCR (European Network of Cancer Registries), IACR (International Association of Cancer Registries), EuroCare (Childhood Cancer Survival in Europe)

>> Join European cohorts of childhood cancer survivors PANCARE (Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer), PancareSurf (Survivor and Follow-up studies)

>> Research network with International studies on risk factors (CLIC Childhood Leukemia International Consortium , I4C International Childhood Cancer Cohort Consortium)

Through its Scientific Committee, Hope-Epi implicates experts in:

>> **Pediatric oncology:** Jean Michon, President of SFCE (Scientific Committee President) ans Pascal Chastagner, President of SFCE scientific board

>> **Epidemiology of childhood cancer:** Jacqueline Clavel (HOPE-EPI coordinator - COHOPER and national registry) and Brigitte Lacour (COHOPER and national registry)

>> **Epidemiology of radiation:** Florent de Vathaire, FCCSS

>> **Quality of life, epidemiology and public health:** Pascal Auquier, LEA

>> **Pediatric hemato-oncologist:** Gérard Michel, LEA

>> **Radiotherapist:** Valérie Bernier, PEDIART

>> And representative of Pancare, ENCCA european projects, Associations of parents and CNAM (health insurance)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Research on the risk factors for childhood cancer, the disparities in cancer management and their determinants, the iatrogenic effects of treatments, the short-intermediate and long term state of health of childhood cancer survivors and the determinants of their quality of life

In consequence, ability to contribute to:

> Primary prevention: prevention of exposure to environmental risk factors, genetic counseling and screening for genetic risk factors

> elucidation and prevention of potential inequalities in healthcare access related to social or territorial characteristics

> reduction of the diseases induced by treatment: screening for sequelae, and contribution to personalized follow-up of iatrogenic risks

> improvement in the management of cancer survivors

> improvement in the quality of life of cancer survivors

> improvement in treatments and post-marketing surveillance: risk/benefit ratio of future treatments through enhanced anticipation of their long-term effects

INNOVATIVE SCIENTIFIC FEATURES

> Data collected thanks to the development or enrichment of the high-performance tools held on a single platform

> Provides researchers with registry, virtual biological collection and cohort data subject to high quality requirements

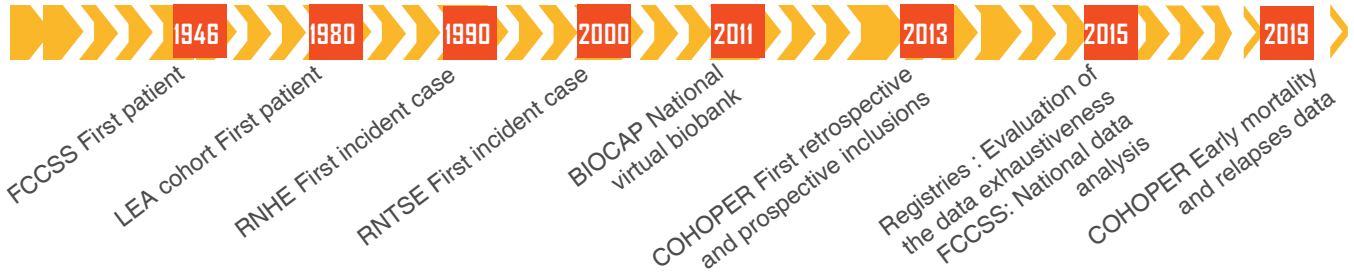
> Promotes the exchange of knowledge between epidemiology, fundamental, biology, genetics, clinical research and human and social sciences

METHODOLOGY QUALITY

> Control of exhaustiveness based on the registry, implemented by capture-recapture by independent sources

> Procedures for a qualified cancer registry: cross checking with clinical trial protocol, histology databases… (increase the number of sources)

DESIGN, METHODOLOGY & TIMELINE



*FCCSS: French Childhood Cancer Survivor Study / LEA: cohort of Childhood hematopoietic malignancies / RNHE: National Registry of Childhood Hematopoietic Malignancies
RNTSE: National Registry of Childhood Solid Tumors / COHOPER: National follow-up of childhood cancer

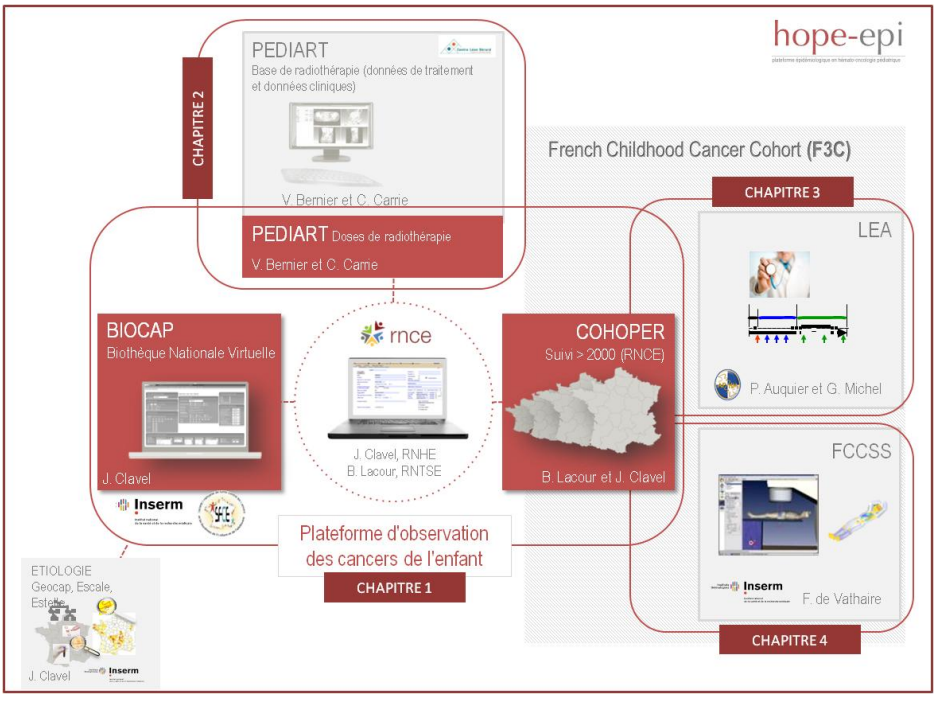
Recruitment objectives: 35 000 cancer cases in 2020 since 2000

Sites: 40 centres
60 - 80 laboratories

Inclusion criteria:
> <18 years
> All cancers in compliance with national and international criteria
> France and overseas departments (Guyane, Réunion, Martinique, Guadeloupe)

INCLUSION COLLECTION
Database: Socio-demographic, socio-economic, diagnosis, treatment, relapse, health care system
Biobank: Virtual biobank samples

FOLLOW-UP: 3 YEARS AFTER DIAGNOSIS
Database: Socio-demographic, socio-economic, treatment, relapse, health care system, quality of life, medical records, questionnaires and medico-administrative database
Biobank: Virtual biobank samples



DATABASE & BIOBANK CONTENTS

Database

>> Registry (RNCE: all incident cases of childhood cancers): identification, vital status (CéPiDC), diagnosis, care trajectory, treatment (protocol), second cancers and relapses before age of 18

>> COHOPER (all cancers since 2000): vital status, details of treatments (chemotherapy, radiotherapy, surgery…), response to treatments, relapses, detection of secondary events (medical records, linkage with health insurance data: SNIIRAM, questionnaires)

>> FCCSS (solid tumors before 2000): radiotherapies administered initially and for relapses (excluding palliative care), treatment plans, copy of the digitized images (DICOM)

>> LEA (leukemias and lymphomas before 2000): socio-demographic and socio-economic (child and family), clinical and therapeutic, organic sequelae, psycho-behavioral and cognitive development, quality of life, access to care and satisfaction

Biobank

Virtual Biobank: The data downloaded from the biological collections will transit under secure conditions via the registry which will identify them, conduct quality controls and add a set of standardized data derived from the registry. The data will then be downloaded as an anonymous formatted set to the virtual biological collection base. The objective is to afford researchers rapid access to information on the availability of constitutional, tumor and peri-tumor specimens with annotations from the registry

>> From the biological collections of the hospital pathology, biology, cytology and hematological cytogenetics laboratories

>> Standardized information on constitutional, tumor and peri-tumor specimens with annotations (from the registry): type, storage, size, quality (reference INCa)

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>> Amigou A, Rudant J, Orsi L, Goujon-Bellec S, Leverger G, Baruchel A, Bertrand Y, Nelken B, Plat G, Michel G, Haouy S, Chastagner P, Ducassou S, Rialland X, Hémon D, Clavel J. Folic acid supplementation, MTHFR and MTRR polymorphisms, and the risk of childhood leukemia: The ESCALE study (SFCE). Cancer Causes Control 2012;23(8):1265-77.

>> Orsi L, Rudant J, Bonaventure A, Goujon-Bellec S, Corda E, Evans TJ, Petit A, Bertrand Y, Nelken B, Robert A, Michel G, Sirvent N, Chastagner P, Ducassou S, Rialland X, Hémon D, Milne E, Scott RJ, Baruchel A, Clavel J. Genetic polymorphisms and childhood acute lymphoblastic leukemia: GWAS of the ESCALE study (SFCE). Leukemia 2012.

Clinical development

>> Desandes E, Bonnay S, Berger C, Brugieres L, Demeocq F, Laurence V, Sommelet D, Tron I, Clavel J, Lacour B. Pathways of care for adolescent patients with cancer in France from 2006 to 2007. Pediatr Blood Cancer 2011.

Outcomes research

>> Alloin AL, Barlogis V, Auquier P, Contet A, Poiree M, Demeocq F, Herrmann I, Villes V, Bertrand Y, Plantaz D, Kanold J, Chastagner P, Chambost H, Sirvent N, Michel G. Prevalence and risk factors of cataract after chemotherapy with or without central nervous system irradiation for childhood acute lymphoblastic leukaemia: An LEA study. Br J Haematol 2013.

>> Berbis J, Michel G, Chastagner P, Sirvent N, Demeocq F, Plantaz D, Barlogis V, Contet A, Poirée M, Kanold J, Galambrun C, Baumstarck K, Chambost H, Auquier P. A French cohort of childhood leukemia survivors: Impact of hematopoietic stem cell transplantation on health status and quality of life. Biol Blood Marrow Transplant 2013;19(7):1065-72.

>> Girard P, Auquier P, Barlogis V, Contet A, Poiree M, Demeocq F, Berbis J, Herrmann I, Villes V, Sirvent N, Kanold J, Chastagner P, Chambost H, Plantaz D, Michel G. Symptomatic osteonecrosis in childhood leukemia survivors: Prevalence, risk factors and impact on quality of life in adulthood. Haematologica 2013;98(7):1089-97.

>> de Vathaire F, El-Fayech C, Ben Ayed FF, Haddy N, Guibout C, Winter D, Thomas-Teinturier C, Veres C, Jackson A, Pacquement H, Schlumberger M, Hawkins M, Diallo I, Oberlin O. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: A retrospective cohort study. Lancet Oncol 2012;13(10):1002-10.

>> Haddy N, Mousannif A, Tukenova M, Guibout C, Grill J, Dhermain F, Pacquement H, Oberlin O, El-Fayech C, Rubino C, Thomas-Teinturier C, Le-Deley MC, Hawkins M, Winter D, Chavaudra J, Diallo I, de Vathaire F. Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality. Brain 2011;134(Pt 5):1362-72.

>> Minaya P, Baumstarck K, Berbis J, Goncalves A, Barlesi F, Michel G, Salas S, Chinot O, Grob JJ, Seitz JF, Bladou F, Clement A, Mancini J, Simeoni MC, Auquier P. The caregiver oncology quality of life questionnaire (cargoqol): Development and validation of an instrument to measure the quality of life of the caregivers of patients with cancer. Eur J Cancer 2012;48(6):904-11.

RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> Identification of **environmental risk factors** (exposures of the residence to radon, high-voltage power lines, road traffic, nuclear site, household waste incinerators, and other industrial sites)

> Identification of **genetic risk factors:** (Genetic polymorphisms, gene-environment interactions)

> Contribution to basic research projects by the BIOCAP virtual biobank

Clinical development

> Observational clinical research

> Access to care and social inequalities: identification of potential limitations in access to care after the initial diagnosis or during relapses, the differences in management and their social and territorial determinants

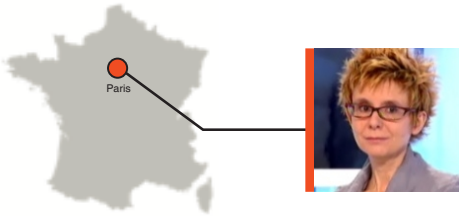
Outcomes research

> Pharmaco-epidemiological studies: drug safety, “real-world” use, effectiveness, practices patterns, acceptance, risk/benefit, risk management.

> Long-term effects, sequels: data on the risk of second cancer and long-term effects (e.g. heart diseases) post-chemotherapy and radiotherapy

> Quality of life studies: state of health, psycho-behavioral and cognitive development, quality of life, management and access to care

MELBASE :
FOLLOW-UP OF A NATIONAL COHORT OF MELANOMA STAGE IV AND UNRESECTABLE STAGE III PATIENTS



Céleste Lebbe
University Hospital Physician and Professor of Dermatology, Head of the Skin Cancer Unit in the Department of Dermatology, Saint Louis Hospital Paris

OVERVIEW

AT A GLANCE

> Oncodermatology
> Melanoma
> Patients with unresectable stage III or stage IV melanoma
> Coordinated by Céleste Lebbe
> AP-HP Sponsorship
> Funded by INCa

KEY FACTS & FIGURES

> Status: Inclusion ongoing
> 1 000 patients to enrolled
> 135 patients already included
> 3 years follow-up
> Multicentric cohort with 25 centres around France
> Biobank with primary melanoma, metastatic sample, plasma, DNA, blood leukocyte pellets

Personalized medicine in advanced melanoma is no longer a dream. It is just beginning and needs to be further developed. Since melanoma is a complex cancer with multiple mutational drivers, resistance is common and multitargeted therapy will be required.

This will rely on new clinico-epidemiological studies and on biological studies aiming to validate and identify new prognostic and predictive factors. Constitution of the advanced melanoma cohort , MELBASE, will provide clinical and histological data, genomic host and tumor alterations, tumor microenvironment characteristics, individual immunological profile and functional imaging to support theses studies. Large biobanks collecting data from MELBASE are mandatory for such projects.

MELBASE is a French national multidisciplinary cohort whose objectives are:

>> To provide an annual instrument pannel with a descriptive and correlative analysis of patients with advanced melanoma in France including epidemiological, clinical and biological socio-economic charateristics

>> To validate and identify new clinical, epidemiological, and biological prognostic factors such as genomic host and tumor alterations, tumor microenvironment characteristics, individual immunological profile in advanced melanoma

>> To evaluate the risk-benefit, the impact on treatment on patient quality of life, the management cost of patients treated with the validated and future treatments of metastatic melanoma.

>> To define predictive biomarkers of response and toxicity including pharmacogenetics and tumor genetics alterations, tumor microenvironment characteristics, individual immunological profile.

Translational Research Clinical Development Outcomes Research

Positioning

> MELBASE investigators comprised active members of EADO (European Association of Dermatological Oncologist).

> MELBASE is the first national bioclinical database on advanced melanoma in France.

LEADERSHIP

MELBASE's leadership team is set up with a tandem of 2 clinicians Céleste Lebbé and Brigitte Dréno committed in the field of Oncodermatology during 20 years.

Céleste Lebbe, MD, Ph.D.
University Hospital Physician and Professor of Dermatology,

- **Head of the Skin Cancer Unit in the Department of Dermatology, Saint Louis Hospital Paris**
- **Coordination of clinical research on melanoma in Saint Louis Hospital Paris**
- **Coordination of a platform of melanoma experimental models in INSERM U976**
- **Board member of French society of Dermatology European Society of Dermatological research European Academy of Dermatological Oncology (EADO) (on board), EORTC, SCOPE**

Brigitte Dreno, MD, Ph.D.
University Hospital Physician and Professor of Dermatology,

- **Head of Skin Cancer Unit, Nantes University Hospital**
- **Vice president of INSERM's COSSEC** (Comité d'Orientation Stratégique et de Suivi des Essais Cliniques), **a committee for strategic orientation and clinical trials Follow-up**
- **Director of the centre of Clinical investigative in Biotherapy (Inserm 0503)**
- **Coordinator of the cancer Federation in Nantes Hospital**
- **Head of the GMP centre of cell and Gene and Cell Therapy**
- **Leading expert**
  >> for AERES
  >> for expert High authority of Health in the ORS/RCP melanoma
- **Board member**
  >> Member of the Scientific Council MEDEC, member of the scientific council of AFM. She is member of French, European and international scientific societies such as Skin cancer Foundation, International Acne Global Alliance, European Association of Dermato-Oncology or International Society for cutaneous Lymphomas
- **Award of International Society for Cutaneous Lymphomas - Board of directors**

SCIENTIFIC NETWORK & MANAGEMENT

- **MELBASE investigators comprised active members of EADO (European Association of Dermatological Oncologist)**

- **Through its Directory and Scientific Advisory Board, MELBASE implicates experts in :**

>> **Onco-dermatology:** B. Guillot (Montpellier), T. Jouary (Bordeaux), L. Misery (Brest), E. Maubec (Bichat), JJ. Grob (Marseilles, President of EADO), L. Mortier (Lille), E. Neidhardt (Lyon), S. Dalle (Lyon), L. Thomas (Lyon), MT. Leccia (Grenoble), T. Lesimpleand, A. Dupuy (Rennes), F. Aubin (Besançon), N. Meyer (Toulouse), F. Granel Brocard (Nancy), MF. Avril (Cochin), P. Bahadoran (Nice), C. Lok (Amiens), L. Verneuil (Caen), C. Robert (IGR), P. Saiag (A. Paré) and the 2 coordinators

>> **Methodology:** R. Porcher

>> **Pharmacology:** G. Favre

>> **Medicoeconomic evaluation:** B. Borget (IGR)

>> **Pharmacovigilance issues:** P. Eftekhari (F. Vidal)

>> **Pathology and Biobanking:** J. Benessiano (Bichat), G. Gallot (Nantes), B. Vergier (Bordeaux), A. Janin (Paris), A. de la Fouchardière (Lyon), V. Costes-Martineau (Montpellier), JP. Merlio (Bordeaux), V. Ugo (Brest), D. Figarella Branger (Marseille), C. Libersa (Lille), F. Berger (Lyon), D. Salameire (Grenoble), B. Turlin (Rennes), S. Valmary Deganos (Besançon), P. Brousset (Toulouse), B. Terris (Cochin), P. Hofman (Nice), G. Duverlie (Amiens), F. Galateau Salle (Caen), P. Viehl (IGR), T. Lavabre Bertrand (Nimes), A. Bonnin (Dijon), JF. Emile (A. Paré)

>> **Fundamental research:** L. Larue (Paris), R. Balloti (Nice), C. Aspord (Grenoble), F. Demenais (Paris)

>> **Imaging:** B. Dupas (Nantes), E. Hindie (Bordeaux)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

MELBASE is the first national bioclinical database on advanced melanoma in France, bringing together medical, bioinformatics and scientific expertises. MELBASE will improve epidemiologial and scientific knowledge as well as medical management of metastatic melanoma

It will allow:

> To determine the prevalence of various genotypes according to region, age, primary melanoma characteristics

> Validate the influence of genotypes on melanoma prognosis

> Inform on the impact of genotyping on the management of metastatic melanoma

> Provide new clinical, socio economic, biological (genetic, pathway activation, tumor microenvironment, immunologic) prognostic factors for advanced melanoma

> Provide information on clinical benefit, risk, cost of new therapies

> Evaluate the impact of new therapies and their algorythm (ie ipilimumab before or after targeted therapies) on survival and toxicities

> Develop biomarkers predictive of response and toxicities including pharmaco and immunogenetic markers in order to be able to select patients with decreased risks of severe adverse events and decrease the cost of melanoma managment

> Increase scientific knowledge on the mechanisms of resistance and define new therapeutic targets

INNOVATIVE SCIENTIFIC FEATURES

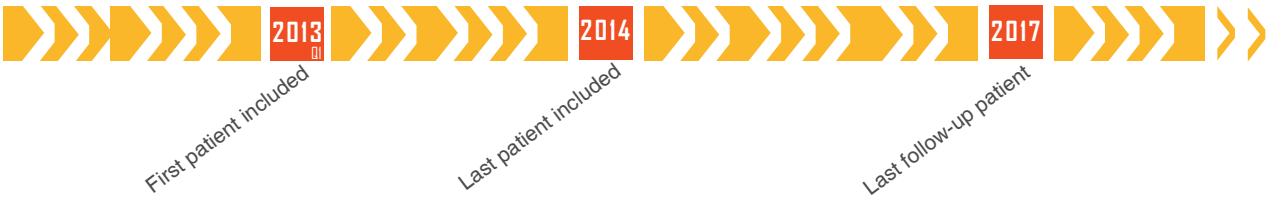
> The clinical database is related to the project CeNGEPS led by B Dreno C Lebbé and A Khamari

> To guarantee the quality of the biobanking process, both the certification and accreditation of the CBRs are based, since 2008, on a Quality Assurance System, according to the French CBR norm NF S 96-900

METHODOLOGY QUALITY

> **Data quality control tools:** Data monitoring, crosschecking with the medical files, controls for coherence at data entry (automated), at file registration (automated) and at file consolidation (by the clinical research assistant), management of doubles for each patients using an adaptation of the Needleman & Wunsch algorithm avoiding doubles at inclusion (automated) and at database consolidation (by the clinical research assistant)

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives: 1 000 patients

Sites: 25 French centres

Inclusion criteria:

> Patients with metastatic melanoma stage IV and with histologic confirmation
> Stage I, II or III melanoma nonoperable
> Age > 18 years old
> Without systemic treatments for inoperable stage III or stage IV outside Adjuvant therapy

Exclusion criteria:

> Choroidal Melanoma
> Stage I, II or III melanoma operable
> Patient refus or patient under administrative supervision

INCLUSION COLLECTION

Database: Clinical constitutional factors, Factors linked to primary melanoma, Factors linked to previous lymph node involvement, Tumor kinetics delay, AJCC stage, Serological markers, Metastatic tumor genotyping, Therapeutic medical, Surgical, Radiotherapic and palliative strategies, Quality of life, Psycho-socio-economic variables, Date of death, Date of latest news.
Biobank: Primary melanoma, Metastatic sample, plasma, DNA, blood leukocyte pellets

FOLLOW-UP : EVERY 3 MONTHS

Database: Clinical constitutional factors, Factors linked to primary melanoma, Factors linked to previous lymph node involvement, Tumor kinetics delay, AJCC stage, Serological markers, Metastatic tumor genotyping, Therapeutic medical, Surgical, Radiotherapic and palliative strategies, Quality of life, Psycho-socio-economic variables, Date of death, Date of latest news.
Biobank: Plasma, DNA, blood leukocyte pellets (every 6 months)

DATABASE & BIOBANK CONTENTS

Database

> **Clinical constitutional factors:** age, gender, phototype, sun exposure, naevotype, body mass index, past history of other cancer, of auto-immune disease, family melanoma history, current medications for other diseases, place of birth and place of current residence

> **Factors linked to primary melanoma:** Breslow index, ulceration, mitotic index, histological type, genotype if available

> **Factors linked to previous lymph node involvement:** micro versus macrometastasis, number and size of nodes, capsular effraction, tumor burden in sentinel lymph nodes. Modalities of elective node dissection

> **Tumor kinetics delay** from first symptoms to primary melanoma diagnosis, delay from primary to stage IV, delay from stage III to stage IV if relevant

> **AJCC stage** at inclusion and after various therapeutic interventions

> **Serological markers:** LDH, S100 if available

> **Metastatic tumor genotyping** (one or more site, one or more time point)

> **Therapeutic** medical, surgical, radiotherapic and palliative strategies with evaluation of response, tolerance, costs (cost of therapy, of radiological evaluations, number and duration of hospitalisation for therapy and-or side effects)

> **Quality of life:** the quality of life scale to be used is not definitively selected yet: it could be either the QLQ-C30 scale from the EORTC (a generic scale evaluating the patient quality of life suffering from a cancer, allowing eventually to compare the quality of life of patients with metastatic melanoma with other localizations) or the FACT-M, a questionnaire specific to melanoma. The EQ-5D scale will also be used to obtain a measurement of utility, used for the calculation of the QALY (Quality Adjusted Life Years). The questionnaires will be administered before the treatment initiation, then as far as possible, every 3 months per year

> **Psycho-socio-economic variables:** family circle, isolation, education, job at inclusion, coping and other psychological factors evaluated with a specific questionnaire

> **Date of death, date of latest news**

Biobank

> A virtual biobank, matched with the clinical data base is implemented. MELBASE biobank relies on the existing national infrastructure for biobanking: the so-called Centres for Biological Resources (CBRs). The CBRs collect, prepare, and store biological specimens of human origin (blood, tissue, cells, cell lines, DNA samples, etc.) and make them available to clinicians/scientists and industrial researchers under specific conditions

> Each patient enrolled in the study has following specimen stored in local CBR:

>> The primary melanoma (mostly paraffin embedded)

>> metastatic sample (paraffin embedded and frozen) from at least 1 site at inclusion and during evolution, particularly before treatment modification if clinically required.

>> plasma, DNA, blood leukocyte pellets, at enrollment and every 6 months for 3 years

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MEMENTO :

DETERMINANTS AND EVOLUTION OF ALZHEIMER'S DISEASE AND RELATED DISORDERS

aviesan
ITMO Santé publique

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OVERVIEW

AT A GLANCE

> Neurology
> Aging & Neuro-degeneration
> Patients with early signs of Alzheimer's disease
> Coordinated by Geneviève Chêne and Carole Dufouil
> CHU Bordeaux Sponsorship
> Funded by Fondation Plan Alzheimer, PHRC

KEY FACTS & FIGURES

> Status: enrolment ongoing
> 1900 already included patients
> 2300 expected enrolled patients
> At least 5 years follow-up
> Multicentric cohort with 30 memory clinic centers in France
> Centralized biobank at Institut Pasteur collecting serum, plasma, DNA, RNA, & CSF

MEMENTO is a comprehensive research platform, organized around a large cohort (2300 patients, 5 years follow-up) of carefully phenotyped patients with early signs of Alzheimer's disease.

MEMENTO specific aims are:
>> Identification of biomarkers for early diagnosis of dementias (Alzheimer, or related disorders)
>> Determinants of transition from cognitive complaint to MCI to dementia and to death
>> Focus on natural history of disease from "preclinical phase" to progression
>> Exploration of vascular and neurovascular patho-physiological processes

Highly standardized assessments:
>> Neuropsychological assessments
>> Neuroimaging (MRI, PET-scan): centralized analysis through CATI (Neurospin)
>> Biobank: Plasma, Serum, CSF, Genetic and Transcriptomic (collection of DNA and RNA)

Translational Research Clinical Development Outcomes Research

Positioning

> MEMENTO is rather unique as a large naturalistic observational study, enrolling patients at an early stage before dementia and with a highly comprehensive and standardized workup (clinical, biological, imaging, socio-economics).

> It is planned to include MEMENTO research platform within some calls of HORIZON 2020.

> MEMENTO collaborates with other national or international projects such as Framingham/Dementia Project.

LEADERSHIP

Geneviève Chêne, Biostatistics and Public Health, Professor

- Teaches clinical epidemiology at the Bordeaux School of Public Health, including e-learning since 2001
- Head of an Inserm team on HIV (U897)
- Head of EUCLID, a F-CRIN services platform for clinical trials
- Coordination of large scale studies including EU-funded collaborations
- Member of the «Comité des sages» for the National Strategy for health, 2013
- Deputy Chair of the evaluating committee of National Program for clinical research (PHRC), 2013
- Main Collaborations (MRC, UCL, Bristol)

Carole Dufouil, Neuroepidemiology, Director of research

- Co-PI of the 3C study (large population based study on dementia)
- PI of the neuroimaging ancillary study of the MAPT trial (national multi-domain prevention trial of cognitive decline)
- Initiation of an international collaboration on optimizing methods in longitudinal analyses of dementia database (Melodem)
- Collaborations with the Framingham study (Boston university), the Institute of Public Health (Cambridge, UK) and the department of epidemiology (UC San Francisco)

SCIENTIFIC NETWORK & MANAGEMENT

Current collaborations:

>> **EMIF-AD (IMI call 2011):** pooled cohort studies on presymptomatic AD and prodromal AD across Europe for discovery of new biomarkers for AD

>> **Framingham cohort:** determinants of dementia and associated disorders with a special focus on vascular risk factors, temporal trends in dementia, cross validation of neuroimaging biomarkers between Memento and Framingham

Future collaborations:

>> **Mayo Clinic Study of Aging,** Rochester, Minnesota, USA: To replicate in a different setting (population based study) and different country findings from Memento

>> **Center Brain Health,** New-York, USA: To set up ancillary studies to test the added value of novel biomarkers

Trough its international scientific committee, MEMENTO implicates experts in:

>> **Geriatry:** Pr Françoise Forette (Co-Chairman)
>> **Public Health:** Pierre Ducimetière (Co-Chairman) & Joël Ménard
>> **Basic science:** Mony de Leon
>> **Social sciences:** Lisa Berkman
>> **Neurology:** Ronald Petersen & Hugues Chabriat
>> **Biostatistics:** David Clayton
>> **Neuroimaging and biomarkers of AD:** Philip Scheltens
>> **Neuroepidemiology:** Annick Alpérovitch
>> **Genetics:** Philippe Amouyel

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Identification of early biomarkers predictive of future dementia

Secondary objectives:

> Provide an extensive characterization of the natural history of well phenotyped patients with early potential signs of Alzheimer

> Investigate neuro-vascular components of the physio-pathological process

> Document the socio-economic burden of this condition for patients, caregivers and society

> Provide for a national integrated research platform with standardized clinical, biological and imaging assessments

INNOVATIVE SCIENTIFIC FEATURES

> The largest naturalistic study of neurodegenerative dementia with a rigorous cohort design

> Extensive follow-up (> 5 years)

> Multiple biomarkers assessed with standardized acquisitions and analyses

METHODOLOGY QUALITY

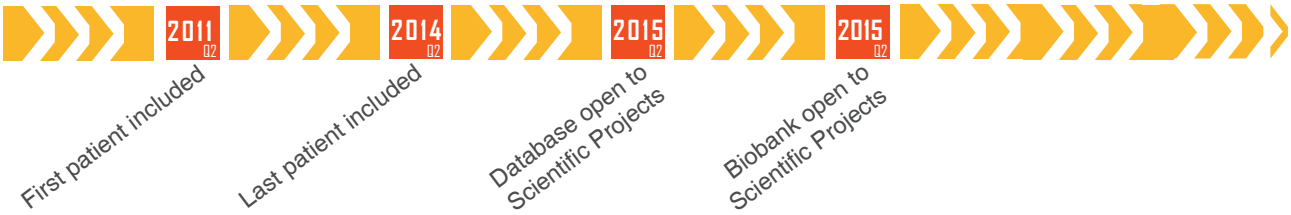
> Harmonization and Standardization of assessments

> E-CRF and robust data-monitoring

> Certification of imaging centers

> Centralized biobank and neuroimaging (Neurospin)

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives: Approximately 2300 consecutive individuals recruited

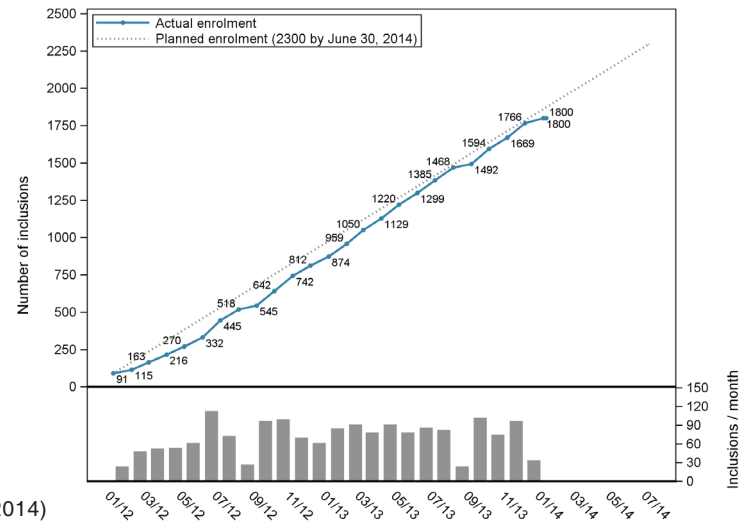
Sites: 27 centres in France (Memory Research Centers)

Inclusion criteria:
> Adults
> Either a recently evaluated (< 6 months) cognitive performance worse than one standard deviation to the mean in one or more domains or an isolated cognitive complaint (patient aged ≥ 60 years).
> Non-demented Clinical Dementia Rating Scale (CDR) <=0.5

Exclusion criteria:
> Guardianship
> Meeting brain MRI exclusion criteria or refusing MRI
> Illiteracy

INCLUSION COLLECTION
Database: Cognitive testing, cognitive complaints, psychopathology, social & human sciences,
Vascular damages
Biobank: CSF sampling, 18F-FDG PET, Amyloid PET, blood sampling

FOLLOW-UP: TWICE PER YEAR
Database: Every year: Cognitive testing, cognitive complaints, psychopathology, social & human sciences
Vascular damages (at 2 years)
Biobank: Every 2 years: CSF sampling, 18F-FDG PET, blood sampling
Amyloid PET (at 2 years)



Enrolment curve (Jan. 6th 2014)

DATABASE & BIOBANK CONTENTS

Database

> The database is comprehensive with a clinical assessment of patients every 12 months, for at least 5 years

> Type of data include clinical assessment, memory tests, neurological and psychiatric assessment, biological sampling (blood, CSF), imaging (MRI, PET-scan), socioeconomic data (burden of disease), QoL, social sciences (social and family environment, caregiver's assessment) etc…

> Linkage of the database with other databases

>> Medico Administrative database SNIIRAM: in progress

Imaging is performed at inclusion and every 24 months - Accreditation of Imaging centres, centralized imaging analysis through Neurospin CATI (Saclay)

> Cerebral MRI

>> 3D-T12D, T2 FLAIR, 2D-T2* (GRE) + phase, 2D-T2 TSE/FSE 1 echo, Resting state (BOLD EPI) , Diffusion (DTI – DWI EPI)

> Visual assessment recorded in e-CRF

> Quality assessment of each sequence with automated test procedures + report

>> Automated analyses: brain tissues and hippocampus volumes, global and ROI-based cortical thickness, gyrification index, fold opening

> FDG PET

>> Harmonization using phantoms

>> Optimisation of reconstruction parameters

>> Automatic quantitative analysis

Biobank

> BCSF, blood, serum, plasma, DNA RNA – performed at baseline and every 24 months

>> Serum: 12 aliquots 0.25 mL

>> Plasma EDTA: 8 aliquots 0.25 mL

>> Whole blood lithium heparin: 2 aliquots of 1 mL

>> Plasma heparin: 4 aliquots of 0.25 mL

>> EDTA blood plasma free: 1 aliquot of 3 mL

>> EDTA blood lithium heparin without plasma: 1 aliquot of 3 mL

>> Tempus: 2 tubes of 9 mL

>> CSF: 16 aliquots of 0.25 mL

> Biobanking is performed according to state-of-the-art processes. Sampling is done at each center, storage and analysis is centralized.

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Clinical development

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Identification and validation of new biomarkers or combination of biomarkers** for the early diagnosis of Alzheimer's disease and associated disorders

> **Identification of prognosis factors for transition** from isolated cognitive complaints to mild cognitive impairment to dementia

> Validation of **surrogate markers of Alzheimer's disease** for future clinical trials

> **Validation of preclinical** and pre-dementia stages of Alzheimer's disease

Clinical development

> Definition phenotypes of patients at high risk of clinical dementia that should be **the target of future clinical trials**

> **Structuration of clinical research** in the field of Alzheimer's disease

> **Platform for clinical research**

Outcomes research

> Better characterisation of etiologies of dementia

> Pharmaco-economic studies cost/benefit of new biomarkers for AD.

> Provide **data to health authorities on the added value of biomarkers** for care and treatment of patients

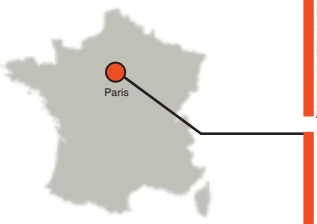
> Assess the **impact of early diagnosis** of AD on the patient and its family

RADICO
RARE DISEASE COHORTS

aviesan
ITMO Santé publique

Jérôme WEINBACH
Science & Operation Director

Serge AMSELEM
Scientific Coordinator



Annick CLEMENT
Scientific Co-coordinator

Paul LANDAIS
Scientific Co-coordinator

OVERVIEW

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AT A GLANCE

> Rare Diseases (RD)
> Coordinated by Serge Amselem, Paul Landais, Annick Clement, Jérôme Weinbach
> Inserm Coordination
> First cohorts start production phase in Sept 2014

KEY FACTS & FIGURES

> Status: first inclusions in 2015
> Potentially any RD patient could be enrolled
> At least 4 years follow-up (depending on each cohort)
> Mostly multicenter cohort, eventually with foreign clinical centers (e.g. EC H2020 project)
> Biobank possible
> Administrative database linkage planned with EPF and BNDMR

RaDiCo is a centralized platform leading the French national program for rare disease (RD) cohorts. It provides a unique set of integrated resources, tools and know-how to set-up and manage cohorts of RD patients and a unique desk to better exploit the generated knowledges & databases.

RaDiCo is based on unique model based on centralized but mobile team and resources for developing as many cohorts as possible in the field of RD. RaDiCo aims to set up reference for the use of common standards for enabling interoperability between existing databases and registries including in the context of transnational cooperation, common thesaurus and ontology, also in line with European and international standards (e.g. Orphanet, Eurordis and IRDiC).

RaDiCo also aims to develop:
>> R&D on ontology and semantic aspects,
>> New approaches & tools for collecting data (active patient, mobile applications, e- and m-Health, telemedicine).
>> Public-Private Partnerships for building RD cohorts and data exploitation.

Translational Research Clinical Development Outcomes Research

Positioning

> There is no other similar RD cohorts program in France or in Europe.

> RaDiCo actively develop European projects and partnerships (e.g. H2020).

LEADERSHIP

RaDiCo's leadership team is set up with a unique set of expertise including genetics, Pr. Serge Amselem, epidemiology, Pr. Paul Landais, clinics & coordination of RD Reference center, Pr. Annick Clement, and coordination of complex, multipartner-projects (Jérôme Weinbach). They are all committed in their respective field for more than 15 years.

Serge Amselem, molecular geneticist, Head of research unit U933 Inserm/UPMC

- Expertise in human molecular genetics
- Head of a molecular diagnostics laboratory and director of an Inserm/UPMC research unit devoted to the study of several RD.
- Coordinator of a University Hospital Department (DHU) on inflammatory and autoimmune diseases.

Annick Clement, pediatrician, Head of pulmonary pediatric department

- Expertise in pediatric lung diseases
- Coordinator of the French Reference center for Rare Lung Diseases
- International collaborations in respiratory medicine: FP7 and North American programs

Paul Landais, epidemiologist, clinical research department Head

- Key experience in the field of clinical cohorts
- National coordinator of the database for rare diseases (BNDMR)
- Close collaboration with the national network of the rare disease centers of expertise
- Creator of the CEMARA network, 61 centers of expertise, more than 200 professionals, 250,000 patients already registered

Jérôme Weinbach, Science & Operations Director, RaDiCo / Inserm

- 15 years experience in international research PPP programs involving patient cohorts / personalized medicine (Nosocomial infections, T1 diabetes, HCV, pediatrics & PUMA, etc.)
- Expert evaluator for the European Commission on transnational e_infrastructures for research communities (ex: toxicogenomics)
- Linked with 17 RD care reference networks on RD

SCIENTIFIC NETWORK & MANAGEMENT

RaDiCo is engaged in the preparation of several key EU project proposals with a Rare Diseases (RD) cohort dimension, which may differ regarding their objectives:

>> proposal for a European platform for facilitated cooperation between Member States' databases and registries on Rare Diseases (interoperability, connectors, standards, resources, clinical research); to be submitted on Sept 2014

>> ICT systems and services for RD integrated care; to be submitted on Oct 2014

post marketing studies & drug development; to be submitted on Oct 2014

>> medico-economic studies / public health and improved patient management. to be submitted on Oct 2014

The RaDiCo platform aligns its standards and activities (and cooperate) with the ORPHANET and EUCERD / IRDiC / EURORDIS international recommendations on databases and data sharing for research purpose, RD classification, database development and cooperation.

Through its Scientific Committee, RaDiCo implicates experts on:

> **Rare Diseases**

>> C. Bodemer, Reference centre for rare genetic dermatologic diseases, Dermatology departments of Necker-Enfants Malades Hospital
>> A. Clement, Reference centre for rare respiratory diseases, Trousseau Hospital, Pierre et Marie Curie University, Paris
>> P. De Lonlay, Reference centre for inherited metabolic diseases, Hôpital Necker-Enfants Malades
>> H. Dollfus, Reference centre for genetic ophthalmologic diseases, Strasbourg Hospital
>> G. Grateau, Reference centre for Amyloidosis of inflammatory origin and familial Mediterranean fever, Tenon Hospital, Paris
>> B. Eymard, Reference centre for neuromuscular diseases, Pitié-Salpétrière Hospital, Paris
>> S. Odent, Reference centre for developmental anomalies and malformation syndromes, Rennes Hospital
>> E. Tournier Lasserve, Reference centre for rare vascular diseases of the brain and retina Lariboisière Hospital, Paris
>> P. Wolkenstein, National Reference Centre for Neurofibromatoses, Henri Mondor Hospital, Créteil

> **Molecular genetics**

>> S. Amselem, Molecular Genetics, Trousseau Hospital
>> C. Boileau, Laboratory of Biochemistry and Molecular Genetics, Bichat Hospital

> **Technological platforms**

>> M.Peschanski, involved for fifteen years in cell therapy for neurodegenerative diseases, head of I-Stem Inserm Team
>> S. Saker, head of the DNA and Cell bank at Genethon

> **Medical informatics**

>> M-C.Jaulent, Datawarehouse, Semantic interoperability, Ontology
>> P. Landais, expert in statistics and computer software developpment

> **Science & Operation Director**

>> Jérôme Weinbach, Science & Operation Director for RaDiCo platform

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Organising prospective & longitudinal phenotypic data collection and data mining tools on rare diseases in France and Europe

Secondary objectives such as:

> Epidemiology
> Innovative ICT tools for empowering patients in data entry and access to information
> Treatment safety. Drug Development. Post marketing studies
> Translational research, phenotypic-genotypic correlations, links with imagery
> Medico-economic studies
> International Cooperation. Capacity Building in countries with no similar infrastructuresfor RD cohorts

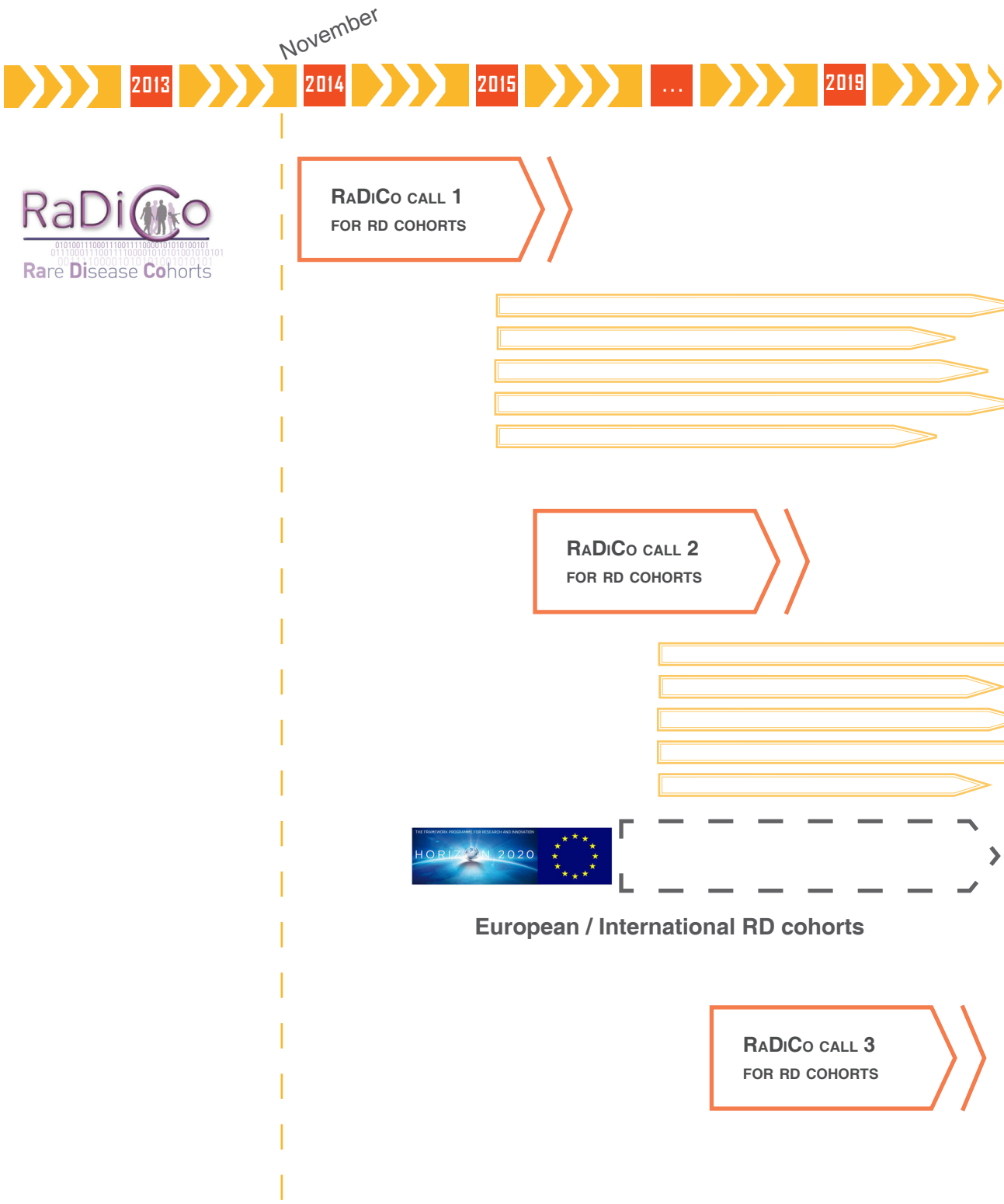
INNOVATIVE SCIENTIFIC FEATURES

> RaDiCo works as a centralized platform hosting all common resources needed for RD database development and utilization in France / in Europe
> Unique ICT solutions for data collection, merging and exploitation including innovative mobile applications for empowering patients and their family in data entry
> Propose user-friendly interfaces for cross analysis of RD data from different sources and fields (phenomic, genetic, imagery, patient data) to accelerate discoveries and knowledge generation

METHODOLOGY QUALITY

> Common databases with technical pre-requisites
> Abide by the highest international standards required for data sharing and RD research (ontology, data security, safety + access)
> A unique legal and regulatory expertise to advise on medical data sharing / exchange and exploitation
> Data standardization and harmonization – interoperability (integration of patient data across disparate systems in France and Europe)
> Links between cohorts data and related biological collections, including IPS cell collections

DESIGN, METHODOLOGY & TIMELINE



DATABASE & BIOBANK CONTENTS

RaDiCo's cohorts fit with any RD medical fields, today organized in France as «Filières de Santé» or national networks of reference centers for RD care

REFERENCE CENTERS NETWORK

- Cardiovascular RD
- Neuromuscular RD
- Kidney RD
- Liver RD
- Developmental RD
- Mitochondiral RD
- Bones RD
- Amylosis RD
- Endocrine RD
- Skin RD
- Head, Neck and Teeth RD
- Sensory organs RD
- Lung RD (non CF)
- Neurovascular RD
- Autoimmune autoinflammatory RD
- Hutington Disease
- Psychiatric RD
- Immuno-Hemato RD
- Hypersomnia RD

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Outcomes research

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RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> Understanding the pathophysiology and natural history of rare diseases (RD), that are also key « models of dysfonction » for more common diseases.
> Identify and validate underlying molecular mechanisms responsible for rare disease onset and progression, as well as phenotypic-genotypic correlations, in order to discover and develop new targeted therapies and diagnostic tools.
> Understanding genetic and environmental factors that may influence the development of RD traits over time.
> Identification of predictive factors for response to treatment through correlation of molecular data (pretherapeutic biopsies) and clinical data with histopathological response in RD patients

Clinical development

> Optimization of clinical studies in the Rare Disease field (timing, measures and scales, sub-population characterization, design…)
> Integrated exploitation of data of different sources (Reference Centers) and nature (phenomic, imagery, genetic, etc.).
> Support clinical enrollment of rare (disease) patients : powerful tools to establish valuable, nation-wide RD cohorts for clinical, epidemiologic and research studies.
> Propose innovative mobile-health solutions and information technology systems to better follow up RD patients regardless of their geographical localization, and collect data more efficiently (e.g. “active patient in data entry”)
> Validation of biomarkers to define clinical stages and improve therapeutic guidance
> Epidemiological studies to support market access

Outcomes research

> Production of optimized or new National RD Diagnostic and Care Protocols (PNDS)
> Standardized procedures and ontology across RD studies, common ontologies (Orphanet, HPO, etc.)
> Pharmaco-epidemiological studies : drug safety, post-marketing studies, orphan drug or ATU designations, “real-world” use, effectiveness, practices patterns, acceptance, risk/benefit, risk management.
> Pharmaco-economic studies cost/benefit; health economic outcomes.
> Comparative studies to assess product efficiency.
> Societal and Quality of life studies (education, employment, medical follow-up) for patients with RD
> Telemedicine, tele-expertise, multidisciplinary consultation, …, solutions assessment and development

UROCCR :
CLINICAL AND BIOLOGICAL NATIONAL MULTIDISCIPLINARY DATABASE FOR KIDNEY CANCER

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CHU Kremlin-Bicêtre –
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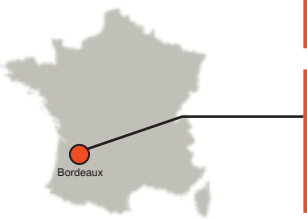


Pr. Nicholas MOORE
CHU Bordeaux –
CIC P0005 – University of Bordeaux

jean-christophe.bernhard@chu-bordeaux.fr

OVERVIEW

AT A GLANCE

> Oncology
> Renal cell carcinoma
> Coordinated by Dr. JC Bernhard
> Bordeaux CHU Sponsorship
> Funded by INCa and the French Urology Association

KEY FACTS & FIGURES

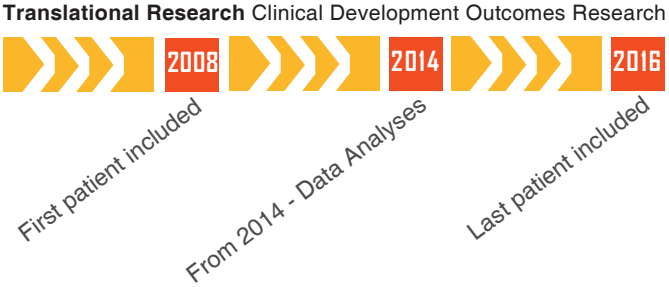
> Status: Inclusions ongoing
> 1 200 already enrolled patients
> About 3 000 expected enrolled patients per year
> Continuous follow-up
> Multi-centric cohort with 15 centers representing third of renal cancer patients in France
> Certified Biobank with tumor and fluids collection

UroCCR provides for a unique and comprehensive clinical research platform on renal cancer patients, not existing elsewhere.

UroCCR is designed with a core standard component across all centres (950 common variables collected) and opportunity for ancillary or complementary data collection in subset of centres.

UroCCR aims to:
>> Set-up of a national network and implement a clinical and biological database of renal cancer patients
>> Develop of multidisciplinary translational research based on careful phenotyping of renal cancer patients and rigorously annotated and certified biobank.

Translational Research Clinical Development Outcomes Research



Positioning

> The project is unique and there is no similar initiative in France or in Europe.

> The UroCCR cooperates closely with the french network of cancer registries (FRANCIM).

> UroCCR is financed thanks to the positive evaluation of INCa in the competitive 2011 call “Bases de données clinico-biologiques” and is also supported by AFU (Association Française d’Urologie)

> There is already a good track-record with industrial collaboration projects.

LEADERSHIP

UroCCR leadership team is set up with a tandem of Urologists, Dr. JC. BERNHARD and Pr. JJ. PATARD, and the renown epidemiologist, Pr. N. MOORE.

Dr. Jean-Christophe Bernhard, MD, Ph.D., Urology PHU – CHU Bordeaux

- UroCCR multidisciplinary design
- Kidney Cancer group of the French Association of Urology Cancerology Committee, Associate member of the European Section of Onco-Urology
- Co-PI of the Robotic Partial Nephrectomy study, Investigator for NEPHRON, AXIPAN, PROTECT phase 3 clinical trial and Global Renal Mass Study (CROES office)
- University of Southern California, L.A, CA (USA)

Pr. Jean-Jacques Patard, MD, Ph.D., Urology PU-PH – CHU Kremlin Bicêtre

- Major experience in collaborative international databases and cohorts
- Head of the Kidney Cancer group of the French Association of Urology Cancerology Committee, European Association of Urology
- PI of the NEPHRON Study, PI of the AXIPAN phase 2 clinical trial, investigator for S-TRAC phase 3 clinical trial
- UCLA, CA (USA), Université de Montreal (Canada)

Pr. Nicholas Moore, MD, Ph.D., Pharmaco-epidemiology PU-PH – CHU Bordeaux

- Clinical Pharmacology
- Post authorisation safety and efficacy studies
- Former president of International Society of Pharmacovigilance (ISOP), VP European Association of Clinical Pharmacology and Therapeutics (EACPT), Director of International Society of Pharmacoepidemiology (ISPE)
- Member of steering group of European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP) at EMA
- 4 FP7 projects with EU-ADR alliance, IMI EU2P, SALT
- Head of 40+ persons operational team in Pharmacoepi/database management

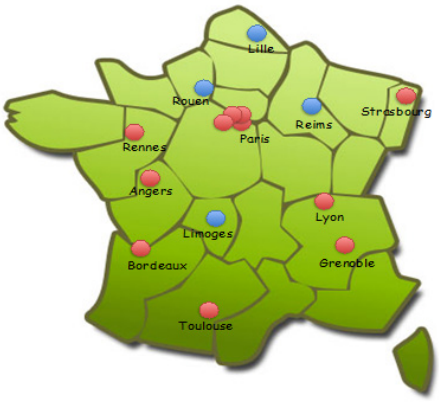
SCIENTIFIC NETWORK & MANAGEMENT

Link with other International Cohorts : Collaboration with University of Southern California (USA)

Governance:

UroCCR Steering Committee

> Coordinator: Dr. Jean-christophe BERNHARD
> Co-Coordinator: Pr. Jean-Jacques PATARD
> Project manager: Mme Magali ROUYER
> Clinical Research Office of CHU de Bordeaux representative
> Local coordinators of multidisciplinary clinical teams:
>> **CHU de Toulouse :** Pr Michel SOULIE
>> **HCL** : Pr Philippe PAPAREL
>> **CHU de Rennes :** Pr Karim BENSALAH
>> **HEGP :** Pr Arnaud MEJEAN
>> **CHU d'Angers :** Dr Pierre BIGOT
>> **CHU de Strasbourg :** Pr Hervé LANG
>> **CHU de Grenoble :** Dr Jean Alexandre LONG
>> **CH Saint Joseph :** Dr Hervé BAUMERT
>> **CHU Mondor :** Pr Laurent SALOMON
>> **UBxS :** Pr Nicholas MOORE
>> **Réseau FRANCIM :** Dr Pascale GROSCLAUDE
> Invited members :
>> **Head of the Cancerology Committee of the French Association of Urology**
>> **INCa** representative: Mr Pascal BOUCHER
>> **Cancéropôle GSO** representative: Mme Maya LAURIOL
>> **ARTuR** representative: Dr. Bernard ESCUDIER



PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

The primary objective of UroCCR is by setting-up a common clinical database and biobank to build a medico-scientific network of multidisciplinary clinical centres dedicated to therapeutic management of patients with renal cancer and a global integrated research platform on renal cancer

Secondary objectives are:

> Study the natural history of disease and clinical/surgical management of patients
> Evaluate treatment modalities: efficacy and safety, clinical trials, targeted therapies
> Translational research: biomarkers, genomics, anatomo-pathology
> Medico economic studies

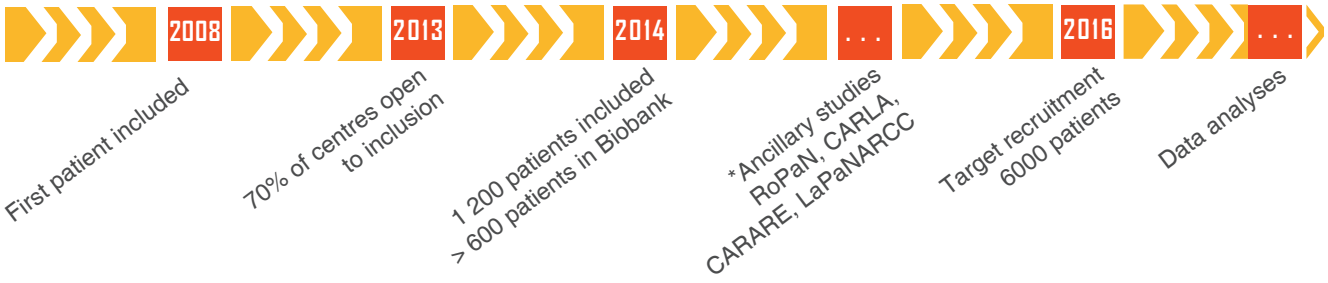
INNOVATIVE SCIENTIFIC FEATURES

> A network of excellence with multidisciplinary expertise
> High potential for translational research
> Unlimited long-term follow-up
> Flexibility to accept new research projects

METHODOLOGY QUALITY

> A decentralized platform, secured web-access for each center
> Rigorous quality control and SOPs
> Carefully annotated and certified biobank, with broad scope

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives: The goal is to recruit at least 6 000 patients

Sites: 15 multidisciplinary centres. Altogether a potential to see 40% of renal cancers in France

Inclusion criteria: All renal cancer patients (localized, locally advanced or metastatic disease) seen in the centres and who give Informed Consent

Exclusion criteria: Lack of Consent, differential diagnosis

INCLUSION COLLECTION
Database: A set of 950 common variables collected for all patients. Addition of set of supplementary variables according to research projects (flexibility for ancillary research)
Biobank: Tumor tissue, healthy surrounding tissue, blood, urine

FOLLOW-UP :
All patients to be followed for unlimited duration, according to current practice in the centre

**Ancillary Studies and associated Projects:*
RoPaN: *Robotic Partial Nephrectomy prospective study*
CARLA: *Cancer and Targeted therapies: survey of Late Adverse events*
CARARE: *Rare Kidney Cancers French Network*
LaPaNARCC: *International cohort on Laparoscopic Partial Nephrectomy fot the treatment of the Agressive Renal Cell Carcinomas.*

DATABASE & BIOBANK CONTENTS

Database

>> Administrative, socio-demogaphic data

>> Clinical data

>> Extensive description of cancer features (clinical, biological and radiological data)

>> Follow-up of the patient and patient care (surgery, oncology treatments with targeted therapies and/or immunotherapy, other local treatment and supportive care, etc…

>> Lifelong Follow-up until death

>> Linkage of the data base with French registry FRANCIM. Linkage with other data bases (CéPiDC, PMSI, SNIIRAM) can be envisioned.

>> CT-scans and/or MRI data description are currently available for > 600 patients

Biobank

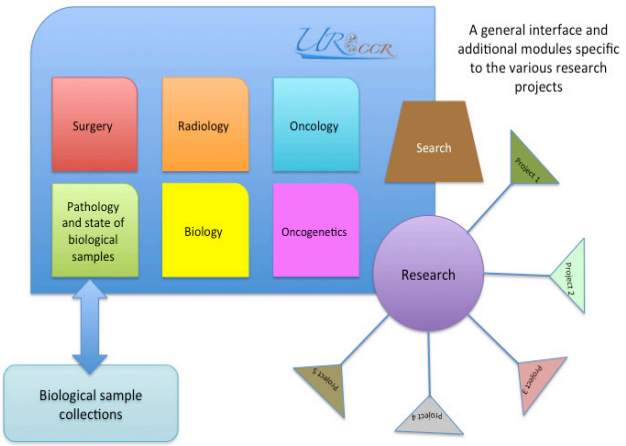
>> Samples are collected according to the Biological Resources Centers or tumor biobanks in each centre

>> Tumor (primitive or metastases) and normal tissue samples are collected after surgery

>> Cryopreserved + FFPE tumor and normal kidney tissue samples for > 600 patients as of today.

>> As of today there is an extensive plasma and urine collection (before and after surgery and at different times during follow-up – 1 month after primary tumor treatment, recurrence, under targeted therapy) for more than 260 patients

>> Possibility for RNA/DNA extraction, IHC, Elisa on fluid samples…



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Translational research

>> Renal cell cancer in young adults: Prevalence, characteristics, and impact of Xp11.2/TFE3 translocation carcinoma diagnosis [EAU meeting, 2013]

>> Predictive factors of impaired frozen kidney tissue samples quality in the setting of outine surgical activity [AUA meeting, 2013]

Clinical development

>> RLe projet UroCCR : de la base de données multicentrique pluridisciplinaire au réseau national médicoscientifique [Correspondances en Onco-Urologie 2012]

Partial nephrectomy for renal tumors of more than 7 cm: Oncological, morbidity and renal function outcomes [EAU meeting, 2013]

Outcomes research

>> Intérêt des bases clinico-biologiques en pharmaco-épidémiologie : la base UroCCR pour la surveillance des effets indésirables des thérapies ciblées utilisées dans le cancer du rein métastatique (étude CARLA Rein) [Poster Journées CGSO 2013]

RESEARCH COLLABORATION OPPORTUNITIES

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

Translational research

> **Identification of biomarkers** for the development of diagnostic or prognostic tests based on the correlation of biological and clinical data

> **Pathophysiology studies** for the understanding of disease history (etiology)

> Development and validation **of novel measurement scales and disease models**

Clinical development

> **Validation of biomarkers** to define clinical stages and improve therapeutic guidance

> **Optimization of clinical studies** (timing, measures and scales, sub population characterization, design….)

> **Support clinical enrollment**

> **Epidemiological studies** to support market access

Outcomes research

> **Pharmaco-epidemiological studies:** drug safety, “real-world” use, effectiveness, practices patterns, acceptance, risk/benefit, risk management

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

> **Comparative studies** to assess product efficiency

> **Quality of life studies**

AERES

stands for Agence d'Evaluation de la Recherche et de l'enseignement supérieur -or Evaluation Agency for Research and Higher education
As an independent administrative authority set up in 2007, the AERES is tasked with evaluating research and higher education institutions, research organisations, research units, higher education programmes and degrees and with approving their staff evaluation procedures.

ANR

stands for Agence Nationale de Recherche -or French National Research Agency.
The ANR is a research funding organisation. The Agency was established by the French government in 2005 to fund research projects, based on competitive schemes giving researchers the best opportunities to realise their projects and paving the way for groundbreaking new knowledge. The role of the Agency is to bring more flexibility to the French research system, foster new dynamics and devise cutting edge-strategies for acquiring new knowledge. By identifying priority areas and fostering public-private collaborations, the ANR also aims at enhancing the general level of competitiveness of both the French research system and the French economy.
Project-based research funding is well established in many countries where it is known to stimulate research organisations and strengthen their synergies. The ANR's approach to funding allows French research to reinforce its international position and better integrate the framework of European cooperation.

ANRS

stands for Agence Nationale de la Recherche contre le SIDA: National Agency for Aids and Viral Hepatitis Research
Created in 1992 by the French government, the Anrs coordinates and funds public research on AIDS and viral hepatitis:
- Vaccine research
- Basic research
- Clinical, therapeutic and epidemiologic research
- Research in public health and the human and social sciences
- Research in developing countries.

ANSM

stands for Agence Nationale de sécurité du médicament et des produits de santé -or French National Agency of Medicine and Health Products Safety. As a public body under the supervision of the Ministry of Health, the ANSM conducts expert assessment of healthcare products and acts as a decision-making body in the field of sanitary regulation. Their aim is to reconcile patient safety with access to therapeutic developments. In France, the Agency works in close collaboration with many institutional partners: other healthcare agencies, Regional Health Agencies (ARS), the French National Health Insurance Fund for Salaried Workers (Caisse nationale de l'assurance maladie des travailleurs salariés – CNAMTS), the French National Authority for Health (Haute Autorité de Santé – HAS), etc.

Aviesan / ITMO Santé Publique

The French National Alliance for Life and Health Sciences (Aviesan)
Aviesan has been set up in response to the commitment to further step up these French research performances by fostering its consistency, creativity and excellence. This mission calls for scientific coordination of the main research themes – which concern all organizations – as well as operational coordination of projects, resources and funding. The purposes of Aviesan are to:
• coordinate the strategic analysis, scientific programming and operational implementation of life and health science research;
• give a fresh boost to translational research by speeding up the transfer of fundamental knowledge to clinical application;
• increase cross-disciplinarity by opening biology and medicine up to contributions from mathematics, physics, chemistry, information technology, engineering sciences, human and social sciences;

	• ensure that projects are consistent in thematic and infrastructure terms; • carry out clinical, economic and social promotion of knowledge, particularly by facilitating industrial partnerships; • define shared standpoints in terms of European research and international cooperation; • harmonize and cut down on red tape for laboratories so as to free up the creativity and excellence of teams. These objectives will be performed within 10 thematic multi-organization institutes (ITMOs) whose primary role will be to chair the strategic debates within their own scientific community. The ITMO Public health works on facilitating and coordinating the activity of research teams who develop studies on public health or clinical research.
Biomedicine Agency	The French Biomedicine Agency is a public organisation under the supervision of the Minister of Health, operating in four key areas of human biology and medicine: assisted reproductive technologies, prenatal and genetic diagnosis, embryo and stem cell research, and the procurement and transplant of organs, tissues and cells, previously entrusted to L'Etablissement français des Greffes (the French Transplant Agency) between 1994 and 2005. These medical activities present major therapeutic, health and ethical issues. Interacting with society, the agency's mission is to provide professionals and researchers with collective answers to the questions they encounter. Its underlying goal is to improve care for patients. The French Biomedicine Agency was created by virtue of the Bioethics Law of August 6, 2004. It guarantees equity, ethics and transparency for the activities under its responsibility, and for anticipated developments.
BIOBANQUES infrastructure	BIOBANQUES infrastructure takes French collection of biological resources to a new level of coordination, quality and efficiency, by setting up a sustainable infrastructure that provides new services, better access for users from public and private sector, develop public private partnerships, interface with the pan European infrastructure BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) and EMbaRC (European Consortium of Microbial Resources Centres) /MIRRI (Microbial Resource Research Infrastructure) and support French biobanks and mBRCs (microorganisms Biological Research Centres) in increasing the value and the use of their collections.
Cancéropole (ex: CLARA, GSO, GO, GE, Nord, IdF, PACA)	Canceropole Lyon Auvergne Rhône-Alpes: The introduction of new players that are the National Cancer Institute and Cancéropôles meets the objective of the cancer plan to mobilize and organize capabilities in cancer research. Their role is to encourage the creation and strengthening of structures pooled research by bringing together expertise and technical resources, to the emergence of thematic research networks, and ultimately accelerate the cycle of research / innovation / treatment, the benefit of patients, in logic care-research continuum.
CHRU	stands for Centre Hospitalier Régional Universitaire : Regional University Hospital
CHU	stands for Centre Hospitalier Universitaire : University Hospital
CIC	stands for Centre d'Investigation Clinique: Clinical Center of Investigation

Cohorts from «Investissements d'avenir»	The "Investments for the future" programme provides funding for 10 selected cohort studies.
CRA	stands for Clinical Research Associate
European Commission FP5 (EU FP5)	The 5th Framework Programme sets out the priorities for the European Union's research, technological development and demonstration (RTD) activities for the period 1998-2002. These priorities have been selected on the basis of a set of common criteria reflecting the major concerns of increasing industrial competitiveness and the quality of life for European citizens
European Commission FP6 (EU FP6)	The 6th Framework Programme is the European Community Framework Programme for Research, Technological Development and Demonstration. It is a collection of the actions at EU level to fund and promote research.
European Commission FP7 (EU FP7)	FP7 is the short name for the 7th Framework Programme for Research and Technological Development. This is the EU's main instrument for funding research in Europe and it will run from 2007-2013. FP7 is also designed to respond to Europe's employment needs, competitiveness and quality of life.
HAS	stands for The Haute Autorité de santé (HAS) - or French National Authority for Health. Its activities range from assessment of drugs (including reimbursement level definition), medical devices, and procedures to publication of guidelines to accreditation of healthcare organisations and certification of doctors.
INCa	The French National Cancer Institute Created by the Public Health Law of 9 August 2004, INCa has two core objectives: To develop expertise in the field of cancer To provide scientific planning, evaluation and funding for projects.
INSERM	Founded in 1964, the French National Institute of Health and Medical Research (Inserm) is a public scientific and technological institute which operates under the joint authority of the French Ministry of Health and French Ministry of Research.
Investissement d'avenir	With €35 billion in funding for 10 years, the "Investments for the future" programme should provide funding for profitable assets and research and innovation infrastructures which promote economic development. These "Investments for the future" are based on 5 strategic areas, and research plays a key role (second in terms of funding) (Figure 1). The goals are to develop biotechnology, stimulate progress in laboratories of excellence, and promote industrial applications of research. Research credits are allocated through seven priority actions: Technological Research Institutes, Health and biotechnology, Laboratories of excellence, Equipment of excellence, Hospital-University Institutes, Technology transfer acceleration companies, and Carnot Institutes. For each of these actions, cancer research received direct funding from the State that is complementary to the INCa investments. The global "investments for the future" made by the State to projects in the field of cancer are estimated at €315 million

GLOSSARY

ISPED	stands for Institut de Santé Publique, d'Epidémiologie et de Développement -or Bordeaux School of Public Health ISPED, within the Université Bordeaux Segalen, is the first University-based School of Public Health ever created in France. Distinct, though very close to a medical faculty, ISPED aims to help meet the great challenges of contemporary public health: increasing life expectancy, the reform of health systems, the resurgence of infectious diseases worldwide, the impact of industrialisation and globalisation on the environment and the population's health.
Lyon Biopôle	Accredited as a World Class Competitiveness Cluster in 2005, Lyonbiopole, a center of excellence for vaccines and diagnostics based in Lyon, focuses on the fight against human and animal infectious diseases and cancers. It aims to increase the competitiveness of the healthcare companies and the appeal of the Rhone-Alpes region territory, namely in the Lyon-Grenoble area. As an intermediary between the public and private sectors, the cluster works to encourage collaboration in R&D, to assist in the project building, to seek funding, to increase strategic and financial partnerships for the economic and international development of companies, and to provide access to project hosting facilities and shared technological platforms such as Lyonbiopole's Infectious Diseases Center, which opened on 1 April 2009
PHRC programme	stands for Programme Hospitalier de Recherche Clinique: Hospital Clinical Research Program
PMSI	stands for Programme médicalisé des systèmes d'information : Healthcare information systems program. French national medico administrative database which collects data from all hospital data stay either medical surgical or obstetrical stay
RNIPP	stands for Répertoire National d'Identification des Personnes Physiques -or National Directory for the Identification of Natural Persons RNIPP is the model for public service registers. It is regularly updated through statistical bulletins on civil status changes, drawn up and sent to INSEE by municipalities and containing details of births, deaths, recognitions and marginal notes made in birth certificates for persons born in metropolitan France or the overseas departments (DOM)
SNII-RAM	stands for Système National d'Informations Interrégimes d'Assurance Maladie: National Information System Inter Plans Health Insurance. French national medico administrative database which collects hospital and ambulatory care consumption data for all people affiliated to the French social security system.
SOP	stands for standard operating procedure