Organisation of Biomedical Research

- Research organisations:
  - Inserm, CNRS, Institut Pasteur, CEA, IRD (infrastructure, staff)

- Project Funding for biomedical research:
  - ANR (National Research Agency) 250 M Euros
  - PHRC (hospital programme for clinical research) 60 M Euros
  - INCa (Cancer Institute) 80 M Euros
  - ANRS 48 M Euros
  - Private foundations (Genethon, ARC, FRM, Axa, Total, SIDACTION…) 150 M Euros
  - Pharmaceutical Industries
# The French Alliance for Life and Health Sciences: Aviesan

**Created in April 2009**

To coordinate the strategic analysis, the scientific programming and the operational implementation of research

- **Research operating agencies:**
  - Inserm (ANRS & INCA)
  - CNRS life sciences department
  - CEA (atomic energy commission)
  - Inra (national institute for agricultural research)
  - Inria (computer science and automatic control)
  - IRD (research for development)
  - Pasteur Institute
  - CIRAD, Fondation Mérieux, IRBA

- **Universities**
- **Hospitals**

**Aviesan Budget ≈ 2.2 Billion Euros**
€2.2bn
ANRS

- Public Agency aimed at funding and coordinating research in all areas relevant to HIV/AIDS and viral hepatitis
- As of 1st January 2012, an autonomous agency within Inserm
- Annual budget of research: 48 Millions euros (total equivalent to 125 millions euros with salaries)
- Supported by:
  - Ministry of Research (39M€)
  - Ministry of Health
  - Ministry of Foreign Affairs
  - Institutional partners: INSERM, CNRS, Pasteur Institute, IRD, Esther
ANRS Funding Mechanisms

• 2 main calls for proposals/year

• Top-down vaccine research programme

• Clinical Trials: AC5/AC24 committees for approval and funding

• ANRS: essentially only funder for HIV and viral hepatitis research in France

• ANRS: funds research, but not institutions, nor salaries
% Distribution of funds according to research area 2012 (44 M €)

- Basic Science HIV: 14%
- Vaccine HIV-HCV: 12%
- Clinical trials and cohorts (HIV): 26%
- Epidemiology/socio-behavioral science: 7%
- Resources limited countries (HIV-Hepatitis): 22%
- Hepatitis B and C: 19%

GLOBAL HEPATITIS 24% : 11 M €
GLOBAL BASIC SCIENCE : 39% : 17 M €
ANRS «Scientific performance »

- 550 publications/year
- Approximately 50% of publications have IF > 5.
- 1% of ANRS publications are in the top 10 international journals
- 6.2% of ANRS publications (HIV/AIDS and hepatitis) are in the 1% group of excellence (number of citations), higher than the national average in the field of biology/health
- France is ranked 2nd or 3rd international position in the field of HIV and 2nd in the field of hepatitis
### ANRS Scientific Advisory Board

<table>
<thead>
<tr>
<th>2013</th>
<th>Developping Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>2011</td>
<td>HIV Basic Research</td>
</tr>
<tr>
<td>2010</td>
<td>HIV Clinical Research/Social Sciences</td>
</tr>
<tr>
<td>2008</td>
<td>Social Sciences, Co-infection Tuberculosis</td>
</tr>
<tr>
<td>2007</td>
<td>Vaccine/HIV Clinical Research</td>
</tr>
<tr>
<td>2006</td>
<td>Developping Countries</td>
</tr>
<tr>
<td>2005</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

#### Members

- **Chair:** Pr Barré Sinoussi Françoise
- **Co-Chair:** Pr Vella Stéfano

<table>
<thead>
<tr>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcamí José</td>
</tr>
<tr>
<td>Barin Francis</td>
</tr>
<tr>
<td>Ball Andrew</td>
</tr>
<tr>
<td>Davril Juliette</td>
</tr>
<tr>
<td>Douek Daniel</td>
</tr>
<tr>
<td>Fischer Hugues</td>
</tr>
<tr>
<td>Lerderman Michael</td>
</tr>
<tr>
<td>Lert France</td>
</tr>
<tr>
<td>Levrero Massimo</td>
</tr>
<tr>
<td>M’ Boup Souleymane</td>
</tr>
<tr>
<td>Moradpour Darius</td>
</tr>
<tr>
<td>Negro Francesco</td>
</tr>
<tr>
<td>Persiaux Renaud</td>
</tr>
<tr>
<td>Reiss Peter</td>
</tr>
<tr>
<td>Schechter Mauro</td>
</tr>
<tr>
<td>Trepo Christian</td>
</tr>
<tr>
<td>Weller Ian</td>
</tr>
</tbody>
</table>

#### Years

- 2013: Developping Countries
- 2012: Hepatitis
- 2011: HIV Basic Research
- 2010: HIV Clinical Research/Social Sciences
- 2008: Social Sciences, Co-infection Tuberculosis
- 2007: Vaccine/HIV Clinical Research
- 2006: Developping Countries
- 2005: Hepatitis
AGENDA of the ANRS: 4 main priorities for HIV

• Study reservoirs with the objective of eradication or functional cure
• Testing: Novel methods; Early and better treatment
• Prevention of new infection with a biomedical approach
• Develop new vaccine strategies

With a NORTH ← → SOUTH vision
Integrating economic aspects
AGENDA of the ANRS:
5 main priorities for HEPATITIS

1. Molecular mechanisms involved in cell-virus interactions
2. Relationships between fibrosis, inflammation and viral replication
3. Strategic evaluation of new molecules anti HCV (Cohort, coinfections, early access programme...)
4. New tools for prevention
5. HBV Cure
INSTITUTIONAL COLLABORATIONS

**NIH – OAR**: Memorandum of Understanding (Dr Francis Collins) – April 2013

**NIAID**: Statement of Intent (HIV Cure research) (Dr A. Fauci) - July 2012

**NIDA**: participation to the NIDA-ANRS-IAS “HIV and Drug Use Fellowship”

Agreements in preparation:

[Logos of UNAIDS, International AIDS Society, and Bill & Melinda Gates Foundation]
ANRS – EUROPE (EC)

• Eurocoord : Specific Cohorts (HIV-2…)
• HIV Resistance : CHAIN-FP7 (AC11)
• NEAT 001/ANRS 143
• HIVERA : ERA-NET : AIDS research policy
  2\textsuperscript{nd} call spring 2013: HIV Prevention – HIV cure
• EDCTP1 → EDCTP-2
• « Horizon 2020 »

• Vaccine : VRI/EuroVacc
Spotlights:

1. ANRS Vaccine Programme
2. HIV cure research
3. HIV clinical research
4. Viral hepatitis research
5. Research in the South
Spotlight 1:
ANRS Vaccine Programme
ANRS vaccine programme

- Top-to-bottom research programme: from basic science to clinical trials
- Awarded the status of “Laboratory of Excellence” in March 2011
- Coordinated by the Vaccine Research Institute
- 10% of global ANRS budget
Development of an epitope-based vaccine approach that could be employed in prime-boost strategy combined with recombinant viruses aimed to elicit strong, long lasting, polyepitopic T-cell responses focused on highly conserved epitopes.
Spotlight 2:

ANRS and HIV Cure Research
### HIV cure: 2-models

<table>
<thead>
<tr>
<th>Eradication</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilizing cure</td>
<td>Functional cure</td>
</tr>
<tr>
<td>Elimination of all HIV-infected cells</td>
<td>Long-term health without cART</td>
</tr>
<tr>
<td>HIV RNA &lt; 1 cop/mL</td>
<td>HIV RNA &lt;50 cop/mL</td>
</tr>
<tr>
<td>Berlin Patient post-BMT</td>
<td>Elite controllers Post-cART controllers</td>
</tr>
</tbody>
</table>
Post-treatment Controllers: new hope for a functional cure

Mississippi Baby

- Infant treated with early, intense antiretroviral treatment within 30 hours of birth.
- Plasma HIV RNA undetectable, despite ART discontinuation…but eventually relapsed

ANRS Visconti cohort

- Long-term remission of 14 patients treated at ~39 days p.i. for a median of 3 years and controlling off therapy for > 4 years
Long-term Remission of HIV after Interruption of Very Early ART in Adults-ANRS EP47 VISCONTI

The probability of patients treated since PHI for >12 months to control for >24 months after treatment interruption is ~ 8-15%.

Hocqueloux et al 2010; Goujard et al 2012; Saez-Cirion et al 2013

EP 47 VISCONTI: 14 patients treated at ~39 days p.i. for a median of 3 years and controlling off therapy for > 4 years

Post-treatment controllers do not have a favorable MHC background

Low reservoir levels which further decreased after treatment interruption in some cases
Prospects for achieving sterilizing or functional cure of HIV infection

- Purging the HIV latently infected cells reservoir (responsible for residual viremia in cART treated patients)
- Targeting a residual virus-producing reservoir with immunotoxin (targeted cytotoxic therapy)
- Manipulating HIV-specific immune responses (including HIV therapeutic vaccine)
- Silencing the expression of HIV genes
- Bone Marrow transplantation (CCR5 delta 32 deletion)

- Prospects for purging the HIV latently infected, quiescent CD4 T cell reservoir
- Progress in HIV gene therapy
An ANRS funding international consortium
France, Germany, Italy, USA, Austria

Treatment with Gene-modified Hematopoietic Stem Cells May Definitively Abolish HIV-1 Infection
Marina Cavazzana-Calvo
ANRS funding for HIV Cure

• Although no specific earmarked funds for HIV Cure, the ANRS funds numerous projects

• Funding, including basic research, preclinical studies and clinical research (therapeutic trials and cohorts)

• 2012 for specific HIV Cure research (very narrow definition) and HIV controllers: **1,4 million € (1,8 M USD)**

• Total amount includes some post-doc salaries and PhD studentships, but excludes all other salaries
Scientific coordination surrounding HIV cure

• **AC 32: Viral reservoirs**
  – Co-presidents: Christine Rouzioux, Hopital Necker, Paris and Asier Saez-Cirion, Institut Pasteur
  – Created in 2008, this group brings together research from basic sciences, preclinical and clinical studies.
  – 4 meetings per year

• **AC 5: Therapeutic clinical trials**
  – President: Jean-Michel Molina, St Louis Hospital, Paris
  – Review and discussion of all therapeutic clinical trials, including trials on primary infection, treatment intensification, etc…
Selected key projects

- ANRS CO6 Primo cohort: *some rare patients show persistent control of HIV following treatment interruption (Antiviral Therapy 2012)*
- ANRS 147 Optiprim: *Evaluation of treatment intensification at AHI on viral reservoirs (poster presentation at ICAAC 2012)*
- ANRS CODEX CO21 - *Multicentric Cohort of HIV Patient With Extreme Profile*

- More than 30 ongoing projects in basic science

- *Pediatric cohort in Sub-Saharan Africa: HIV+ infants treated within one month of life.*
ANRS and the International Scene of HIV Cure research

NIAID: Statement of Intent (HIV Cure research)  
(Dr A. Fauci) - July 2013

Member of IAS Towards an HIV Cure Advisory Board
Spotlight 3:
ANRS and HIV Clinical Research
New Challenges: HIV and emerging new diseases...

- Cancer, lymphomas
- Ageing diseases
- Cardiovascular diseases

Immune defects, Inflammatory and autoimmune malignancies

HIV Infection
- Chronic on HAART
- Non AIDS related mortality

Learning from each other beyond HIV/AIDS......
HIV Clinical Research
Key figures in 2013

- Network of 150 clinical centers (36 Centers : 79% of inclusions)
- More than 10,000 patients enrolled in studies sponsored by ANRS
- **Ongoing** - 15 clinical trials, 14 cohorts in HIV and 1 in HIV-HCV coinfection, 6 physiopathological studies
- **In the near future** – 3 clinical trials, 3 physiopathological studies
- 76 FTE of « MEC/MEB »
- 28 % of ANRS total budget (2.1 M extra ANRS: EC, Pharmaceutical Industry)
- 5 CTUs
Main Research Fields

• **Mother-child, pediatrics** (ANRS 128 Penta 11, ANRS 135 Primeva, ANRS 150 Penta 18, ANRS CO1 EPF, ANRS CO10 Enfants infectés, ANRS CO11 Observatoire, ANRS CO19 Coverte)

• **Primary infection & treatment initiation** (ANRS 141 Tipi, ANRS 142 Start, ANRS 147 Optiprim, ANRS CO6 Primo, ANRS CO9 Copana)

• **Infection control/Functional Cure** (ANRS CO18 HIV Controller, ANRS CO21 Codex, ANRS EP47 Visconti, ANRS EP49 Evarist)

• **Antiretroviral strategies** (ANRS 140 Dream, ANRS 143 Neat 001, ANRS 146 Optimal, ANRS 157 ROCnRAL, ANRS 159 VIH-2, ANRS CO14 IL-2)

• **Comorbidities** (ANRS 144 InterACTIV, ANRS 148 Liveral, ANRS 153 Treve, ANRS 154 Lenakap, ANRS CO16 Lymphovir, ANRS CO17 Vihgy, ANRS EP45 Aging, ANRS EP48 HIV Chest)

• **Co-Infections HIV/HCV/HBV**: CO13 Hepavih, Phase 2 Trials

• **Others** (ANRS CO3 Aquitaine, ANRS CO4 FHDH, ANRS CO5 VIH-2, ANRS, ANRS EP46 Novaa, ANRS EP50 Orivao)
Ongoing Trials

- **Primary Infection**
  - ANRS 147 Optiprim: intensified Rx in primary infection

- **Naive Patients**
  - ANRS 143 / NEAT 001: RAL + DRV/r in naive
  - START / ANRS 134: When to start ART 120 pts in France
  - ANRS 146 OPTIMAL: intensification with maraviroc on clinical outcome

- **Treatment Experienced Patients**
  - ANRS 140 Dream: PI monotherapy vs EFV
Ongoing Trials 2

- Trials in Specific Groups of Patients
  - ANRS 148 Liveral: PK RAL in liver failure
  - ANRS 153 Treve: RAL in renal transplant recipients
  - ANRS 159 VIH-2: RAL in HIV-2 pilot study
  - ANRS 135 Primeva: LPV/r monotherapy in pregnant women
  - ANRS 144 Interactiv: varenicline for smoking cessation
Trials in Preparation

Maintenance therapy

- Phase II trial with RAL + ETR
- Phase II trial in pts with low plasma viral load
- Phase II trial with intermittent dosing in well suppressed pts (4 days/week): 4D
- Phase II trial with low dose Darunavir
- Phase II trial with dolutegravir + 3TC
HIV Prevention Trial in high risk MSM
Conflicting Results with Daily Oral PrEP

- FTC/TDF for HIV discordant couples (Partners PrEP)
- TDF for HIV discordant couples (Partners PrEP)
- TDF for young heterosexuals (TDF-2)
- TDF/FTC for injecting drug users (Bangkok TDF)
- TDF/FTC for MSM and TW (iPrEx)
- TDF/FTC for women (FEM-PrEP)
- TDF for women (VOICE)
- TDF for women (VOICE)

**Efficacy (95% CI)**
- FTC/TDF for HIV discordant couples (Partners PrEP): 75% (55; 87)
- TDF for HIV discordant couples (Partners PrEP): 67% (44; 81)
- TDF for young heterosexuals (TDF-2): 63% (22; 83)
- TDF/FTC for injecting drug users (Bangkok TDF): 49% (10; 72)
- TDF/FTC for MSM and TW (iPrEx): 44% (15; 63)
- TDF/FTC for women (FEM-PrEP): 6% (-52; 41)
- TDF for women (VOICE): -4% (-49; 27)
- TDF for women (VOICE): -49% (-129; 3)

Effectiveness of “on demand” PrEP Randomized placebo-controlled trial

- High risk MSM
- Condomless anal sex with ≥ 2 partners within 6 m
- eGFR > 60 mL/mn

Full prevention services*
TDF/FTC before and after sex (n=950)

Full prevention services*
placebo before and after sex (n=950)

- Counseling, testing for STI, condoms, vaccination, PEP
- Primary endpoint: HIV infection
- Incidence of HIV-infection: 3%PY, 50% efficacy, 64 events
- ~ 2000 pts
## Declining Acute HIV Infections in iPrEx

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Prevalence Antibody-RNA+</th>
<th>Fold Decrease (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4%</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Follow-up:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.1%</td>
<td>3.8 (1.5 to 9.5)</td>
<td>P=0.004</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>0.06%</td>
<td>6.5 (2.2 to 20.2)</td>
<td>P=0.002</td>
</tr>
</tbody>
</table>

Marcus JL et al Plos one 2013; 8:e81997
Ipergay Time-Lines

- Trial was designed before Caprisa 004 and Iprex results were available
- Gay community involvement and Community Advisory Board
- Decision to launch the trial after the results of all PrEP trials were released
- Pilot phase in 3 sites in France (Paris, Lyon) to ensure feasibility and secure funding
- First patient randomized February 22, 2012 in Paris
- Canadian Trial Network is partnering with ANRS and trial has received IRB approval
- Trial extension in France (Lille, Nantes, Nice) and Germany (Berlin) with the support of the Gates Foundation
Spotlight 4: ANRS and Viral Hepatitis Research

- Budget increase from 5% to 24% of total ANRS budget (2005 to 2012)
- Mono infection and HCV/HBV HIV co-infection
- North and South
HEPATITIS CO-INFECTION / NEW DRUGS

- **ANRS HC26 « TELAPREVIH »**: Pilot Study of PegInterferon-Ribavirin-Telaprevir Efficacy and Tolerability in HIV-HCV Coinfected Patients Who Had Previously Failed a PegInterferon-Ribavirin Regimen

- **ANRS HC27 « BOCEPREVIH »**: A pilot study to assess the efficacy and the safety of Boceprevir in combination with PegInterferon alfa and Ribavirin, in subjects with HCV/HIV coinfection, in failure to a previous therapy of Peginterferon/Ribavirin

- **ANRS HC30 « QUADRIH »**: Pilot study to assess the efficacy and safety of a Quadruple therapy with Asunaprevir, Daclatasvir, Ribavirin and pegylated Interferon alpha2a, in HIV and HCV genotype 1 or 4 co-infected patients, previously null responders to a standard Pegylated interferon – Ribavirin regimen

- **ANRS HC 31 « SOFTRIH »**: Pilot study assessing efficacy and tolerance therapy oral therapy with Sofosbuvir/ledispavir fixed dose in co-infected VIH-VHC genotype 1 patients, failing a triple therapy with NS3/4A protease inhibitor
Spotlight 5:

ANRS and Research in the Global South
8 research sites
- Cameroon - Cambodia
- Burkina Faso - Vietnam
- Côte d’Ivoire - Egypt
- Senegal - Brazil

Agreement
- Governments / ANRS
- Scientific and strategic agenda defined jointly within national programmes priorities

Goal
- Sustainable support for capacity building, personnel and infrastructure development