EASTERN-FRANCE **CANCEROPOLE**
**CANCÉROPÔLE** DU GRAND-EST

# Core Thematic C

## Viral Infection and Cancer


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# - Viral Infection & Cancer - Presentation

## Context

- **Scope :**
  - Virus-linked cancers : **necessary but not sufficient cause of carcinogenesis**
  - Need : **improving SCREENING and THERAPEUTIC policies**
- **CGE skills :**
  - **Renowned expertise** at national and international levels within CGE
  - Validated **methodologies**, dedicated **platforms**, annotated **cohorts**

**HPV - The transborder CGE-DKFZ Research Program in HPV Tumor Virology (2006-2010)**

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

- **Key figures :**
  - **2** cancers addressed : cervical and skin
  - **6** CGE teams, **1** at IARC and **6** at DKFZ (over **50** researchers and clinicians)
  - A French-German Doctoral College
  - **25** international publications
  - A funding of around **5** Meuros
  - Main orientations : 1) mechanisms of **CARCINOGENESIS**
    2) **NOVEL MARKERS**
    3) **INNOVATIVE THERAPIES**

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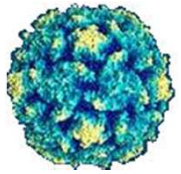
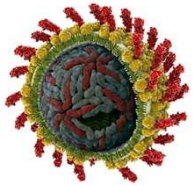
# - Viral Infection & Cancer - C
## Presentation

### Other tumor viruses: EBV and HCV

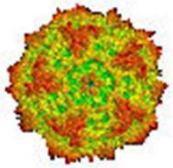


**Epstein-Barr** and cellular microRNAs variations in post-transplantation lympho-proliferative disorders: implication for early diagnosis and development of therapeutic tools (Strasbourg and Paris)



**Hepatitis C** antiviral strategies for preventing hepatocarcinoma (Strasbourg)

### An oncolytic virus: the parvovirus



Early steps of H-1 **oncolytic parvoviruses** infection (Heidelberg and Strasbourg)

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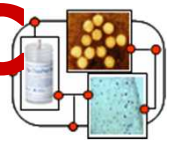
# - Viral Infection & Cancer - 2007-2010 report



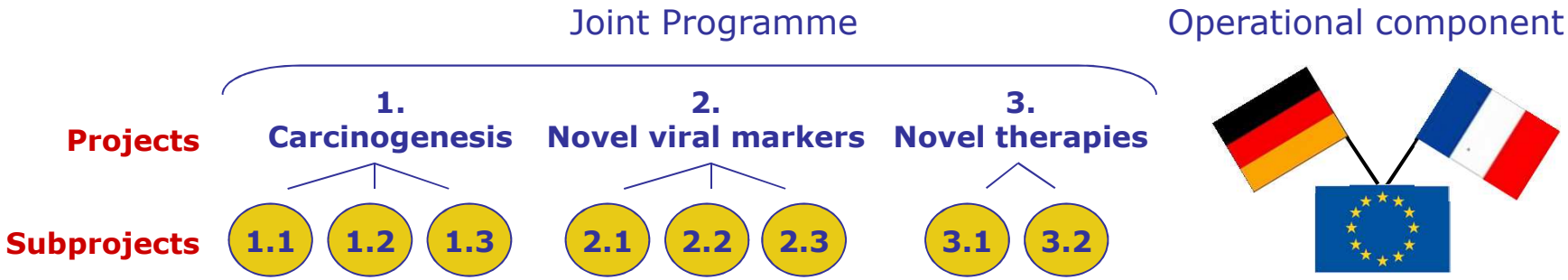
## HPV - The CGE-DKFZ joint program in Applied Tumor Virology — Context and ambition

- **Breakthrough since 2006 :** launching of a prophylactic vaccination program expected to prevent up to 70% of precancerous lesions and cervical cancers

- **Screening policies and therapeutic developments should still be improved :**
  - Women not covered by the vaccination program continue to be at risk
  - There are HPV-associated malignancies not targeted by the vaccine
  - The current vaccines needs to be assessed (longevity, virus escape, …)
  - The vaccines are not designed to exert a therapeutic effect

- **Ambition of the program :**
  - Clarify the mechanisms of tumorigenesis linked to the infection
  - Bridging the gap between molecular virology and patient care
  - Help to improve the quality and costs of patients follow-up and treatment

## HPV - The CGE-DKFZ joint program in Applied Tumor Virology — Operational




- **An effective binational networking :**
  - Mobility of scientists
  - Mutualization of resources (biological materials, platforms, experimental models)
  - Privileged access to longitudinal cohorts and databases
  - Inter-site methodology standardization

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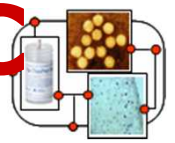
# - Viral Infection & Cancer - 2007-2010 report



## HPV - The CGE-DKFZ joint program in Applied Tumor Virology  Achievements & prospects

### PROJECT 1 - Cell regulatory pathways are involved in HPV-linked CARCINOGENESIS

**1.1** Therapeutic targets for cervical cancer : the Net – c-fos circuit ? ⇨ *Therapies targeting Net and hypoxia pathways*

**1.2** Down-regulation of ligand- and UV-induced apoptosis by mucosal and skin HPV types ⇨ *HPV as a relevant target in skin cancer?*

**1.3** Implication of the HPV oncoproteins E6/E7 in genomic instability ⇨ *Deregulation of p53 and Polo-like kinases contributes to E6/E7-induced genomic instability*

### PROJECT 2 - Immune biology and NOVEL MARKERS for tumor progression

**2.1** Transforming properties and T cell immunology of cutaneous HPV ⇨ *Immune responses in patients* ⇨ *novel anti-HPV cutaneous prophylactic and therapeutic strategies*

**2.2** Viral load, integration & expression of HPV DNA ⇨ *Markers of tumor progression* ⇨ *cost-effective policies*

**2.3**

### PROJECT 3 - INNOVATIVE THERAPIES based on oncolytic H-1 parvovirus (H-1PV)

**3.1** Targeting H-1 PV to cervical-carcinoma derived cells using an adenovirus-H-1PV hybrid vector ⇨ *Improvement of i) vector production, ii) tumour cell transduction & iii) oncolytic effect* ⇨ *Potential for re-targetting*

**3.2** Combinatorial approaches using antineoplastic compounds ⇨ *Synergistic oncolytic effects using Staurosporine / HDIs and H-1PV / HDIs*

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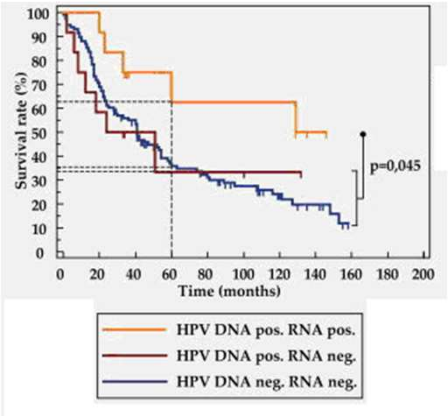
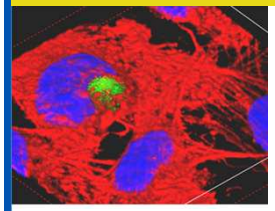
## Other original HPV ongoing projects

### HPV and head and neck squamous cancer (HNSCC) : prognosis improvement

- Analysis of E6/E7 high risk-HPV oncoproteins in HNSCC cancers of 231 patients (14% HPV+) ⇨ The presence of **E6/E7 transcripts correlates with a better prognosis**
- Affymetrix Gene Chip and CGH array genome-wide studies ⇨ The 16q22-24 locus is involved, in particular **APP-BP1** (Jung et al, Int. J. Cancer 2010) ⇨ Analysis of APP-BP1 regulation with in vitro models




### Horizontal transfer of HPV oncogenes : an alternative way to carcinogenesis



- Fibroblasts cultured with **HPV-positive apoptotic bodies** derived from cervical cancer cells are transformed
- **Functional viral sequences** were observed in transformed cells (↓ of p53, target of E6)

⇨ Mechanisms of internalization ?
⇨ Degree of dependence on viral oncogenes of the transformed cells ?
⇨ Tumorigenic potential of the transformed cells ?

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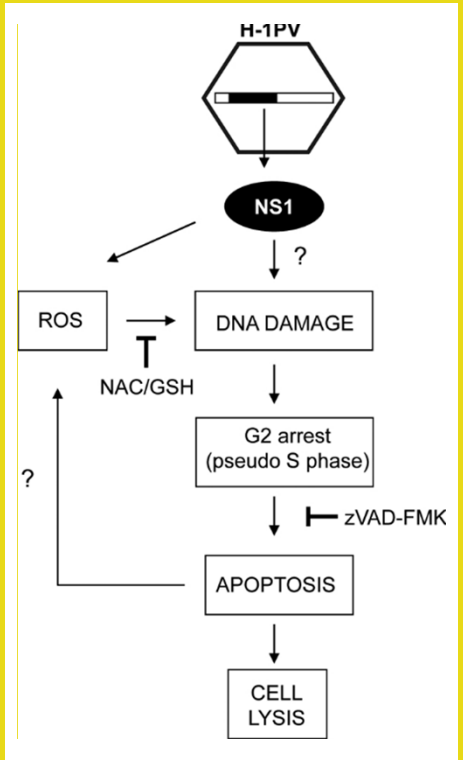
## Parvovirus

### Exploring the early steps of infection of H-1 oncolytic parvoviruses




*Tentative model of H-1PV cytotoxicity (Marchini et al.)*

**Objective :** cellular elements determining the success of H-1PV infection and mediating viral cytotoxicity?

- Discover molecular signatures for predicting PV treatment
- As leads for optimization of H-1PV-based treatments
- As leads for the development of antiviral antidotes

**Approaches :**

- Transcriptomics and ChIP on chip studies (carried out)
- Human Druggable siRNA library screening (carried out)

**Results :**

- Identification of putative NS1 transcriptional targets
- Identification of positive and negative regulators of PV life cycle and cytotoxicity

## Epstein-Barr Virus (EBV)

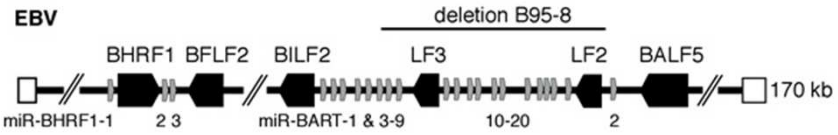
### Impact of EBV on miRNAs expression profiles in post-transplantation lymphoproliferative disorders

**Rationale :** ⇨ EBV encodes its own viral miRNAs

⇨ Cellular miRNAs expression is impacted by EBV infection

**Results :**

- **Differences in cellular and miRNAs expression profiles** after TGF-beta treatment found by sequencing and real time PCR ⇨ Next step : identification of **cellular targets of deregulated miRNAs**
- **Small RNA libraries generated** from primary B cells infected lytically with EBV ⇨ miRNA expression in the early steps of EBV infection ?
- **Patient samples** (tumor biopsies and serum) will serve to estimate the **prognosis power of miRNAs quantification** for lymphoproliferative disorders




*Genomic localization of EBBV microRNAs (Pfeffer et al.)*

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# *- Viral Infection & Cancer -*
# 2011-2014 Action Plan

## Carcinogenesis

- Regulation of p53 and E6/PDZome network in HPV cancer cells
- Persistance & cellular genomic instability by horizontal transfer of HPV oncogenes
- HCV antiviral strategies for preventing hepatocellular carcinoma ⇨ **new project**

## Novel Viral Markers

- Novel HPV markers for cancer diagnosis and progression assessment
- HPV infection in head and neck cancers
- Impact of EBV and cellular miRNAs expression profiles on lymphoproliferative diseases

## Innovative therapies

- Development of novel anticancer therapies based on the use of oncolytic viruses
- Drug design based on novel E6 structural data

## Screening strategies

- Primary cervical screening using HPV testing ⇨ **new project**

plan cancer

## Objectives vs. Plan Cancer

⇨ Strengthen translational research (**Actions 1.1, 1.2**); support clinical research and increase patient inclusions (**Actions 4.1**, resp. **4.2**)
⇨ Study the impact of new HPV research technologies on the global fight strategy against cervical cancer (**Action 16.5**)
⇨ Assist pathology departments integration of scientific and technological innovations (**Actions 20.1, 20.2, 20.3**)
⇨ Improve the access to screening, diagnostic and surveillance (**Actions 21.2, 21.4**)

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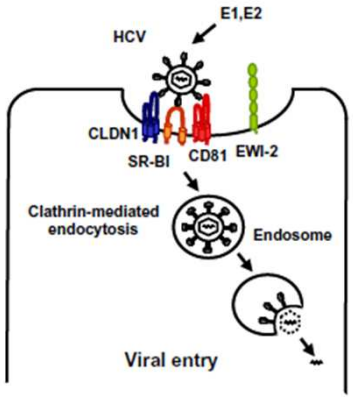
# - Viral Infection & Cancer - 2011-2014 new projects

## Hepatitis C Virus (HCV)

### HCV entry : therapy for hepatocellular carcinoma ?




*Model of HCV entry in a human hepatocyte (Baumert et al.)*

**Previous work** : HT siRNA kinase screening using the retroviral HCV pseudoparticle model ⇨ Receptor tyrosine kinase **EphA2** ⇨ Validation

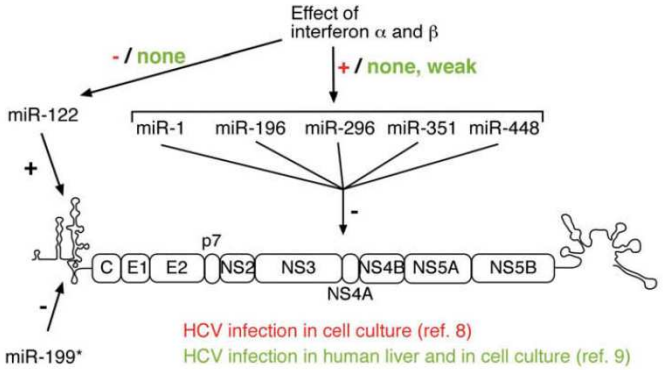
**Aim of the project** :

- Molecular mechanism of HCV-kinase interactions ?
- Impact for hepatocarcinogenesis
- Identification of novel entry factors using siRNA screening with the "druggable genes" library

### Involvement of microRNAs in HCV infection in the host restriction

**Tool** : recently generated mouse cell lines expressing human receptors for HCV

**1st result** : the virus can enter the cells, but not replicate




*known interactions of miRNAs with HCV RNA and the effect of interferon on their expression in vitro and in vivo (Baumert et al.)*

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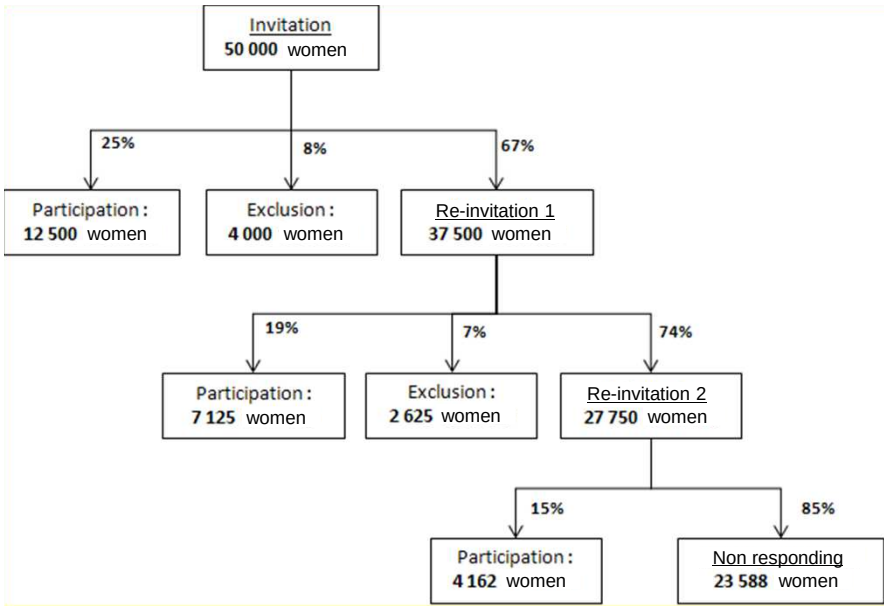
# - Viral Infection & Cancer -
# 2011-2014 new projects

## Primary cervical screening using HPV testing

*This ambitious project is the only one being retained by INCa in response to the August 2010 call « Primary cervical screening using HPV testing »*




➢ **Objectives :**

- Improving in a cost effective manner the screened population coverage while preserving the screening efficacy for participants
- Fight against inequalities with regard to cancer

➢ **Tools :**

- Cytology arm (women 25-30 years)
- HPV arm (women 31-65 years)

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# *- Viral Infection & Cancer -*
# CGE coordination support

## Broadening of the alliance with DKFZ

**Tumor Virology :** part of the broadened collaboration

## Concertation with regional governments

- Strenghtening of the Champagne-Ardenne Hospital Biology Platform
- Acquisition of siRNA libraries (druggable genome, …), contribution to deep sequencing cost
- Strenghtening of the existing –omics / information technologies / cell and animal models facilities infrastructure

## Towards novel HPV screening strategies

Strengthening of the coordination via the recruitment of a part-time project manager for assisting Pr. Christine CLAVEL