Eastern-France Canceropole
From Plan Cancer I
to Plan Cancer II

Inter-regional and crossborder mobilization
towards translational cancer research

Pr. Pierre OUDET
Scientific Director
**Assets:**
- Internationally renowned research centers
- Dense network of registries
- 4 federated Comprehensive Cancer Centers (CCC) and 5 University Hospitals
- Proximity of European reference cancer centers
- Partnership with the Caisse d’Epargne

**Organization: the BUREAU**
- The CGE President (President of an Eastern-France Regional Council)
- The 5 Regional Contact Points
- The CGE Scientific and Administrative Directors
- The Head of the COCLIN (Clinician Committee)

**REGIONAL CONTACT POINTS**: bidirectional information transfer from researchers/clinicians to local authorities and CGE coordination team.
Connector with policy-makers and charities

- **INCa**
  - Contribute to Plan Cancer I and II

- **5 regional governments**
  - Support cancer research emergence
  - Development of high throughput technological infrastructures

- **Ligue contre le Cancer**
  - Setting up of an inter-regional coordination (calls for projects / evaluation)
  - Partnership in the context of the CGE broad public conferences

Joint actions with canceropoles, e.g. with CLARA

- Symposium on nutrition, metabolism and cancer (2009)
- CGE-CLARA-DKFZ symposium on infections and cancer (2010)
Key events:

- **Wide scope cancer research**: annual scientific Forums
- **Translational Research**: OncoTrans
- **Clinical Research**: COCLIN
- **Meetings on Human Sciences & Cancer**
- **General public & health professionals**: annual conferences

Communication strategy and knowledge database:

- Corporate & focused brochures
- Electronic NewsLetter
- CGE web interface:
  - 2 static portals: research / public
  - Relational database dbCGE
- Inter-canceropole communication workgroup animated by CGE

www.canceropole-ge.org
CGE presentation
The dbCGE

Example out of the Actors Directory

People
Hospital/technological ressources
Directories
Calls
News

Coordinates & affiliation
CGE research Axis
Other team’s members
CGE presentation
The dbCGE

Real time list of cancer publications
List of INCa projects
Public access (non confidential information)
Editor access (global information)
Focus on 3 platforms with federative character:

- Transfected Cell Array Platform: 120 K€
- Clinical Proteomics Platform: 120 K€
- Epidemiology Platform: 60 K€
Towards inter-regional structuring:

- **INCa incitement**:
  - Evaluation
  - Scientific valorization
  - Standardized set of clinical data

- **CGE response**: an inter-regional TASK FORCE
  - Centralization of sample data management
  - Implementation of a virtual tumor bank (2009)
  - Establishment of shared collections
  - Setting up of a histopathology hub
  - Training on demand

www.canceropoleyge.org/tvr/
The crossborder alliance with DKFZ

2007-2010: the CGE-DKFZ joint Program in Applied Tumor Virology

2011-2014: broadening to other topics
- Tumor virology (extension to other viruses: HCV, EBV, HPV)
- Stem cells and cancer
- Molecular genetics
- Bio-informatics
- Translational oncology
- Immunogenetics
- Interventional radiology
- Cancer epidemiology

„Dear Prof. Oudet,
I would like to let you know that we support your initiative for joint projects of Cancéropole Grand-Est and the DKFZ to realize the exchange of scientists and the bilateral access to technical platforms and to identify new fields of interactions and collaborations. As a result of the CGE-DKFZ meeting in September 2010 a first concept of a joint project on the immune response against hepatitis C virus has already been developed.

Pr Otmar WIESTLER, CEO DKFZ „
Links with economic development entities and industry:

- **Almetis** (Strasbourg) → Anticancer compounds based on ruthenium
- **OncoDesign** (Dijon) → Design of xenografts models
- **Genclis** (Nancy) → Discovery of a transcription infidelity phenomenon amplified in cancer
- **Transgene** (Strasbourg) → Development of anticancer vaccines
- **Miothéris** (PI: Archamps) → Consortium established for designing multitherapy devices combining pressurized steam and local chemo-/immunotherapeutics
- **Alsace BioValley** → Close association concerning the development of innovations in cancerology
Nonrandom variations in human cancer ESTs indicate that mRNA heterogeneity increases during carcinogenesis

Marie Bruilliard*, Dalia Lorphelin†, Olivier Collignon‡, Walter Lorphelin†, Benoît Thouvenot†, Emmanuel Gothis†, Sandrine Jacquenet§, Virginie Ogier†, Olivier Roitel†, Jean-Marie Monnez‡, Pierre Vallois*, Frances T. Yen*, Olivier Poch§, Marc Guenneugues§, Giles Karcher¶, Pierre Oudet¶, and Bernard E. Ibhai¶*

Genki SAS, 15, Rue du Bois de la Chapelle, 54500 Vandœuvre-lès-Nancy, France; †Institut Ella Carton, Université Henri Poincaré, BP 239, F-54506 Vandœuvre-lès-Nancy Cedex, France; ‡I2BC Lipidomics, Institut National Polytechnique de Lorraine, 15, Rue du Bois de la Chapelle, 54500 Vandœuvre-lès-Nancy, France; §Institut de Génétique et de Biologie Moléculaire et Cellulaire, 1, Rue Laurent Fries, BP 10142, 67404 Illkirch Cedex, France; ¶Canceropole du Grand Est, Hôpital de Hautepierre, 1, Avenue Mollière, 67200 Strasbourg, France; and Kantrie Hospitalier Universitaire de Nancy, 5, Allée du Monen, 54000 Vandœuvre-lès-Nancy, France

Edited by Pierre Chambon, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg, France, and approved March 14, 2007 (received for review December 13, 2006)

From a basic research concept to translational research

Bioinformatics-based screening of accumulated ESTs databases:

- Transcription Infidelity (TI) is a normal phenomenon that is increased in cancer cells
- Gaps are most dramatically increased TI events in cancer cells ➔ frame-shifts

Overproduction of TI proteins by cancer cells causes a shift from innate to adaptive humoral response:

1) appears effective up to a threshold of tumor burden
2) is T and B cell dependant
3) does not require any adjuvant
4) is specifically directed against TIPs
Proof-of-concept ongoing at clinical level

- **Testing for breast cancer using 24 TIPs in combination and support vector machine**

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resubstitution</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>Leave-one-out</td>
<td>95%</td>
<td>92%</td>
</tr>
</tbody>
</table>

- Controls $N=227$
- Breast cancer $N=285 + 2$

![Graph showing distance to SVM hyperplan for controls and cases with breast cancer.](image)

AUC 0.98

**Men with Breast Cancer**
2007-2010 key figures

**Number of PROJECTS**

- **Submitted**
  - 2004-2006: 85
  - 2007-2010: 216
- **Funded**
  - 2004-2006: 31
  - 2007-2010: 73

**Number of TEAMS participating to CGE projects**

- **Applying**
  - CGE Teams: 175
  - Outside Teams: 66
- **Funded**
  - CGE Teams: 219
  - Outside Teams: 89
  - CGE Teams: 45
  - Outside Teams: 33

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Comparative analysis 2005-2009:

- **Examples of prominent publications reflecting CGE activities:**
  - Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. Guiu et al, *Gut* 2010  
    - Inter-regional AGARIC project
    - ITAC Platform
    - Xenograft model → phase I trial
    - Selection by COCLIN → CGE support
    - Metabolomics platform
**2011-2014 coordination action plan**

**Inter-regional networks**
Neuro-oncology, oncopediatrics, SHS, Bio-banks, Quality of Life (QoL), interventional radiology, functional genomics, tumor virology

**Partnership with DKFZ**
Tumor virology (HCV, EBV, HPV), stem cells and cancer, molecular genetics, bio-informatics, translational oncology, immunogenetics, interventional radiology, cancer epidemiology

**Platforms: support, follow up**
Metabolomics (CARMeN), radio-biology, xenografts, QoL

**Economic and clinical valorization**
Links with the competitiveness poles and the clinical research support units

**Thematic meetings**
Biomarkers, anti-PARP, COCLIN

**Wide scope meetings**
Scientific Forums, OncoTrans

**Sensibilization of the broad public**
Conferences dedicated to the broad public and health professionals

**Training support**
Participation of young scientists and students to:
- International meetings
- training courses (DIU, DU, Masters)
**Targeted topic** : translational research in oncology
**Process** : annual call for proposals
**Support** : 500 euros per candidate (10 per year)
**Research within CGE**

**PROCAN I (2007-2010)**

1. Epidemiology: health indicators and practice evaluation
2. Infections and Cancer
3. Local control of tumors
4. Control of the tumor dissemination
5. Understanding and overcoming therapeutic failures
6. Immunomolecular and cellular approaches

**PROCAN II (2011-2014)**

**A**
- Health indicators, Epidemiology, Human & Social Sciences

**B**
- Translational Research – Biomarkers, Imaging technologies, Early Clinical Trials

**C**
- Viral Infection & Cancer

**D**
- Cancer Functional « - Omics »

**E**
- Immunity & Cancer
Core Thematic A

Health indicators – Epidemiology – Human and Social Sciences

Pr Jean FAIVRE
(INSERM-U866, Dijon)

Pr Francis GUILLEMIN
(INSERM CIC-EC, Clinical Epidemiology Center, Nancy)

Pr Didier TRUCHOT
(EA3188, Laboratory of Psychology, Besançon)
Epidemiological surveillance of cancer in France

FRANCIM network of cancer registries

- Incidence-prevalence
- Health care practices
- Survival
- Screening Evaluation

General
Specialised
National
(children solid tumours + multiple endocrine neoplasia)
### Estimated number of new cancer cases in France

<table>
<thead>
<tr>
<th></th>
<th>1980</th>
<th>2005</th>
<th>Variation</th>
<th>2010 (projection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>170 000</td>
<td>320 000</td>
<td>+ 89 %</td>
<td>360 000</td>
</tr>
<tr>
<td>Prostate</td>
<td>10 700</td>
<td>62 200</td>
<td>+ 481 %</td>
<td>71 500</td>
</tr>
<tr>
<td>Breast</td>
<td>21 700</td>
<td>49 800</td>
<td>+ 129 %</td>
<td>57 800</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>23 800</td>
<td>37 400</td>
<td>+ 57 %</td>
<td>40 000</td>
</tr>
<tr>
<td>Lung</td>
<td>17 900</td>
<td>30 600</td>
<td>+ 79 %</td>
<td>36 900</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3 700</td>
<td>10 200</td>
<td>+ 176 %</td>
<td>10 800</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2 600</td>
<td>7 200</td>
<td>+ 177 %</td>
<td>8 300</td>
</tr>
<tr>
<td>Liver</td>
<td>1 800</td>
<td>6 400</td>
<td>+ 256 %</td>
<td>7 600</td>
</tr>
<tr>
<td>Head and neck</td>
<td>13 300</td>
<td>12 200</td>
<td>- 16 %</td>
<td>11 000</td>
</tr>
<tr>
<td>Stomach</td>
<td>8 900</td>
<td>6 800</td>
<td>- 24 %</td>
<td>6 400</td>
</tr>
</tbody>
</table>
Role of nutritional and environmental factors

<table>
<thead>
<tr>
<th>Colorectal cancer</th>
<th>Hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGARIC (n=496/576)</td>
<td>CIRCE (n=847/1200)</td>
</tr>
<tr>
<td>• <strong>Cases:</strong> surg. for colorectal cancer</td>
<td>• <strong>Cases:</strong> HCC</td>
</tr>
<tr>
<td>• <strong>Controls:</strong> surgery</td>
<td>• <strong>Controls:</strong> Cirrhosis</td>
</tr>
</tbody>
</table>

Grants from Canceropole, INCa, Fondation de France, Ligue contre le cancer
Fatty acid intake (PUFA), adipose tissue metabolism and colorectal cancer (AGARIC Study)

- **Aims:**
  - Role of n-3 and n-6 PUFA, Trans FA, conjugated isomers of LA
  - Role of metabolic syndrome

- **Methods:**
  Evaluation of dietary PUFA intake using 2 biomarkers
  - PUFA composition of erythrocyte membranes
  - PUFA composition of subcutaneous adipose tissue
  - Determination of insulin resistance and adipocytokines levels

- **Collaborations:**
  - Epidemiologists
  - 5 departments of digestive surgery
  - Biologists (gas chromatography analysis, circulating adipocytokines)
Risk factors of liver cancer in cirrhotic patients
(CIRCE Study)

➢ Aims:
  • Role of environmental factors (lifestyle habits, drugs, viruses..) and diet
  • Role of metabolic syndrome
  • Serum/plasma biomarker profiles

➢ Methods:
  • Metabolic syndrome:
    - Adipocytokines
    - Insulin resistance
    - Radiological examinations
  • Nutritional questionnaire and nutrition-related biomarkers
  • Predictive studies by proteomic and vibrational spectroscopy

➢ Collaborations:
  • Epidemiologists
  • 6 University hepatology departments
  • Endocrinologist and nutritionist
  • Radiologists
  • Pharmacologists
  • Biologists (nutrition related biomarkers, polymorphisms)
  • Platforms of proteomic and vibrational spectroscopy
Mass screening for colorectal cancer (CRC)

The Burgundy study was at the origin (with a UK and Danish study) of the inscription of CRC screening in the European Code Against Cancer, of the Statement of the European Commission and decision to implement CRC screening in France (effective since 2009).

- Evaluation of a qualitative immunochemical test:
  - Better sensitivity than the Hemoccult® test (Eur J Cancer 2008)
  - Comparable performances of available tests

- Protein biomarker signature for improving CRC screening

- Collaborations:
  - Epidemiologists
  - Public health specialists
  - Health economists
  - Gastroenterologists (public and private practice)
  - GPs
  - French screening network
  - Biologists (mass spectroscopy, ELISA tests)
Clinical Research Platform labelled by Ligue Nationale contre le Cancer since 2008 based on the network of the epidemiological and statistical units from CGE

Endorsed by the Eastern France Canceropole and its Clinicians committee

Since 2010: structuration into a national platform

Objectives:
- To increase use of QoL as endpoint in oncology trials and epidemiological studies
- To provide methodological expertise for measure and analysis of QoL data in clinical trials and epidemiological studies
- To develop and conduct translational methodological research studies in order to improve our knowledge in that field
- Human and Social Sciences - Combining and networking competences on specialized fields

Platform «Quality of Life and Cancer» (2)

➢ 3 Research Axes:

• **Axis 1:**
  Validation, selection and use of QoL questionnaires
  "Evaluation and validation of quality of life scales in advance palliative stage of cancer patients"

• **Axis 2:**
  Longitudinal QoL analysis:
  “Comparison of modalities for Longitudinal QoL analysis”

• **Axis 3:**
  Prognostic value of QoL and relation with clinical criteria
  "Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma"

➢ Collaborations:

• Epidemiologists
• Biostatisticians
• Clinicians
• Established links with national and international cooperative groups
Medico-economic evaluation of petscan

- **Main objective:**
  - To assess changes in practices of cancer diagnosis and therapy after interregional implementation of petscan and its medico-economic consequences
  - To assess its consequences on patients quality of life

- **Petscan was set in 5 regions** in 2003-2004

- **A quasi-experimental before-after design**

- **Main results:**
  - Modeling cost-effectiveness
    - Solitary pulmonary nodule
    - Potentially operable non-small-cell lung cancer
    - Metachronous liver metastases from colorectal cancer
  - Changes observed in practice
    - Management of solitary nodules
    - Cancer staging
    - Quality of life of patients with solitary pulmonary nodule
  - Actual cost estimate of petscan in French health care system
- Human and Social Sciences -
Access to care

- Burnout in oncology personal: a national study
  **Objectives:**
  1. To assess the association between perceived stressors, coping strategy, emotional work and burnout, among oncology personal
  2. To design a French Stressor Scale and a French Coping Scale for oncology personal
     (Col. Univ-Besançon / Univ-Bordeaux 2)

- Socio-economic status, cancer management and survival
  1. Socio-economic differences in the management of colorectal cancer cases
  2. Factors associated with delays in diagnosis and in treatment

- PRESID: Practice, social representation and incitement to screening:
  **Objectives:**
  To determine representations and attitudes in terms of motivations and barriers towards CRC screening
  (Col. Univ-Paris 8; Aix-Marseille; Besançon)
- Human and Social Sciences -
Conferences and Workshops

➢ Conferences on human sciences and cancerology:
   - 2008: Human sciences and cancerology
   - 2010: Understanding and improving the patient quality of life
   - 2012: Cancer and exclusion

➢ Multidisciplinary workgroups on disparities in cancer:
   • Quality of life
     - Satisfaction with care and quality of life
     - Announcement of palliative care
   • Work and cancer
     - Concerns about returning to work
     - Return to work after cancer
     - Burn-out in health care
- Health indicators, epidemiology, Human and Social Sciences -

Key figures

- Number of teams:
  55 in 2007 - 119 in 2010
  - 12 epidemiologic teams, 31 registries and networks (screening structures, regional oncology organisation)
  - 48 clinical teams, 28 Human and social sciences teams

- Projects funded by INCa:

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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<td></td>
<td>11</td>
<td>7</td>
<td>5</td>
<td>8</td>
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</table>

- Support request: 472.5 K€ for the 2011-2014 period
  - Emerging project "socioeconomic status and cancer management /survival"
  - Network of registries: melanoma observatory (in Champagne-Ardenne)
  - Quality of life platform (recruitment of an epidemiologist)
  - "HSS and cancerology" biannual meetings
Core Thematic B

Translational Research – Biomarkers, imaging technologies and early phase trials

Pr Pierre FUMOLEAU  
(CCC Georges-François LECLERC, Dijon)

Pr Hervé CURE  
(CCC Jean Godinot, Reims)

Pr Jean-Louis MERLIN  
(CCC Alexis Vautrin, Nancy)

Dr Séverine VALMARY-DEGANO  
(Franche-Comté Biobank, University Hospital, Besançon)
Overall objectives:
- Promote the translation of discoveries issued by local teams (academic and/or industrial)
- Accelerate the transfer of innovations to the patient
- Increase the participation to clinical trials

Strategy:
- Increase awareness of available technologies and facilities (optimized use in attractive protocols)
- Support the acquisition of cutting edge technologies and strategies, including Quality of Life approaches
- Promote exchanges among clinicians and with researchers (COCLIN, Forum, Oncotrans)
- Promote early phase clinical trials

Objectives vs. Plan Cancer
- Strengthen translational research (Actions 1.1, 1.2)
- Support clinical research and increase patient inclusions (Actions 4.1, 4.2)
- Promote cancer research coordination in connexion with the policy towards comprehensive cancer research centres (Action 5.2)
- Assist pathology departments integration of scientific and technological innovations (Actions 20.1, 20.2, 20.3)
- Facilitate the access to treatment innovations and early phase trials (chemotherapy/surgery) (Actions 1.3, 21.1, 21.2, 21.3)
- Improve the access to screening, diagnostic and surveillance (Actions 21.2, 21.4)
The CGE Clinician Committee (COCLIN)

- Established in 2006
- Focus on translational research with local/regional interactions
- Transfer between basic and clinical research
- Implementation of protocols for early phase I and II
  - Attractivity and visibility of clinical research protocols of CGE investigators
  - Increase of patient inclusion rates

![Diagram showing phases of translational research and the role of COCLIN](image)
Structuring Clinical Research (1)

- 16 PHRC granted over the 2007/2010 period (7 granted in 2010)
- Steady increase over the past 4 years

Repartition of PHRC PI per Canceropole (%, 2000-2010 period)

<table>
<thead>
<tr>
<th>Year</th>
<th>CLARA</th>
<th>GE</th>
<th>GO</th>
<th>GSO</th>
<th>IDF</th>
<th>NO</th>
<th>PACA</th>
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<tbody>
<tr>
<td>2004</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
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<tr>
<td>2005</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
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<tr>
<td>2006</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
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<td>2009</td>
<td>50</td>
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<td>2010</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
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</tbody>
</table>
Structuring Clinical Research (2)

Comprehensive Cancer Centers (CCC)

Patient inclusion rates in clinical trials in Cancer Treatment Centers

<table>
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<tr>
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<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>9.66% ± 2.87</td>
<td>10.77% ± 3.02</td>
<td>13.29%</td>
</tr>
<tr>
<td>Median</td>
<td>10%</td>
<td>10.21%</td>
<td></td>
</tr>
<tr>
<td>Extremes</td>
<td>3.24% - 14%</td>
<td>3.17% - 15.7%</td>
<td>6.28% - 18.25%</td>
</tr>
<tr>
<td>Eastern-France</td>
<td></td>
<td></td>
<td>13.66%</td>
</tr>
<tr>
<td>Mean</td>
<td>5.88%</td>
<td>8.40%</td>
<td></td>
</tr>
<tr>
<td>Individual rates</td>
<td>3.24% - 4.19% - 6.37% - 9.76%</td>
<td>3.17% - 8.77% - 10.43% - 11.24%</td>
<td>7.98% - 13.71% - 14.67% - 18.25%</td>
</tr>
</tbody>
</table>

University Hospitals

Oncology Department of Besançon University Hospital (Pr X. Pivot)

National ranking (2009):
- CCC Dijon 1st
- CCC Reims 5th
Structuring Clinical Research (3)

- **Early Phase (I/IIa) clinical research units:**
  - Dijon (CGFL), accredited as a CLIP² (Early Phase Investigation Centers) by INCa in 2010
  - Nancy (CHU/CAV)

- **Emergence of Comprehensive Cancer Research Centers (2010 INCa SIRIC Call):**
  2 applications, Dijon and Strasbourg, based on the establishment of Regional Cancer Institutes (IRC) in Burgundy and Alsace, and on the links between the care centers and university research centers

- **« Investissements d’avenir »**
  Numerous applications for equipment and long-term research programs, eg IMAPPI (functional and multimodal imaging, Dijon)
Plugging technological expertises for clinical studies of higher impact
CARMEN (Strasbourg) : Cancer Metabolomics

1st worldwide implementation of a dedicated equipment (HRMAS NMR spectrometer) within the hospital in 2007. Public-private consortium (university hospital, Strasbourg university, CNRS, Bruker Biospin and CGE):

- **Automation** development and industrial application validation (jump from 10 to 30 analyses per day)
- **Metabolic fingerprint** of characteristic tumour phenotypes
- Ex vivo study of the **energetic metabolism** of tumour cells w/o drug/radiation exposure

- >2500 samples profiled, 6 publications.

Cancer Molecular Genetics Platforms

Facilities implemented within the 5 regions, in connexion with a regional network providing access for all patients. Contribution to the national integrated research program on lung cancer (PNES poumon).
CLIPP (Dijon) : Clinical Proteomics

- Emerging **IBiSA platform** (2008), coordination of the **INCa network** for clinical proteomics
- Promotion of the « **Circe ProSpec** » PHRC (identification of biomarkers associated to risk factors of HCC in cirrhotic patients, 2010)
- Developments in **standardisation, data processing and bioinformatics methodologies**, innovative biocaptor design and application to clinical samples, part of a larger research unit with complementary methodologies

Vibrational spectroscopy (Reims)

**Infrared microimaging** as a tool for the characterisation of tissue sections, in addition to **conventional histo-pathology**.

*Wolthuis et al., Anal Chemistry 2008*
Medical Radiobiology (Strasbourg)

- Collaboration of Centre Paul Strauss (CCC) and Aerial (technology resource center).
- Wide panel of capabilities (treatment volume and applications)
  - molecular and cellular mechanisms induced by ionizing radiation
  - anticancer drugs radiosensitization potential
  - development of preclinical models

Emerging project: design and synthesis of bifunctional compounds for radiochemotherapy modalities (platinum salts and PARP inhibitors)

Xenograft platform (Strasbourg/Nancy/Dijon)

Public/private consortium
Collection of human tumor specimen passaged in nude mice (colorectal, brain, lung, kidney, ...)

Application to preclinical studies of
- Drug candidate efficacy
- Drug mode of action/acquired resistance mechanisms

Support data to PHRC « Phase I clinical trial of rapamycin and irinotecan in pediatric patients with refractory solid tumors – RAPIRI » (2010)
Pharmimage (Dijon):
- Clinical and preclinical imaging multimodality facilities (MRI, TEP, SPECT).
- Transdisciplinary public/private consortium from tracer design to image data processing (pharmacology, chemistry, informatics, electronics, physics, biology, nanotechnology and medicine)
- Full dedication to pharmaco-imaging (treatment efficacy monitoring and selection of most relevant molecules)
- Incentive for investment in structuring equipments, such as a cyclotron and a radiochemistry unit (operational in 2011)

Nancyclotep (Nancy):
- PET facility equipped with clinical and small animal imagers
- Implementation of a radiochemistry laboratory for novel tracer research and development
- Support facility for the application as a University Hospital Institute (« IHU ») on « Diagnosis Engineering using Biomarkers and Imaging ».
**Biobank workgroup**

#### Context
- A **network of regional biobanks** supported by INCa
- Involvement in local, national and European projects (eg BBMRI)
- **Data management:**
  - Industry standard compliant Databiotec software
  - Clinical annotations comprising the 40-item set defined by INCa (National Virtual Tumorbank)
- **Shared collections**: head & neck cancers, colorectal cancers, breast cancers, lymphoma, urogenital cancers, mesothelioma and sarcoma

#### Workgroup meetings
- **Heads of biobanks** ➔ overall orientations of the network (mutualised or concerted investments, priority collections, expert identification, ...)
- **Technical staff** ➔ practical questions (quality policy, sample qualifications, ethical issues, ...)

#### Building a virtual histopathology hub
Implement advanced **high-throughput scanning technologies** and data transfer networks, access via a common portal
- **share patient or model files** aggregating pathologic, biologic and clinical data
- **build an image database** (archiving, training...)

*Recruitment of a project manager supported by CGE*

---

*2011-2014 CANCEROPOLE INITIATIVE (PROCAN II) – AERES Audit 9 Feb 2011*
Prognostic and predictive factors, novel biomarkers and therapies

- Integrated approaches for biomarker discovery and validation
  - Molecular profiling of tumours  \( \rightarrow \) Genomic, proteomic, metabolomic molecular platforms
  - Mechanistic studies using cellular and animal models  \( \rightarrow \) Xenografts and basic research laboratories
  - Circulating cells and proteome profiling in the course of treatment \( \rightarrow \) Nancytomics, Clipp
  - Functional imaging approaches  \( \rightarrow \) Pharmimage, Nancyclotep

- Ongoing projects
  - Signalling cascades activation status monitoring in breast cancers (Nancy, Dijon), head and neck cancers (Nancy), colorectal cancer (Nancy)
  - Cancer metabolotheque (Strasbourg)
  - Clinical validation of new cell surface markers in chronic B-cell malignancies (Strasbourg)
  - Molecular probes for imaging (Dijon)
Identification of novel tumor antigen targets for diagnosis and monoclonal antibody therapy

**Aims:**
- Cell membrane targets for the recruitment of antibody dependent cell cytotoxicity (ADCC) and complement dependant cell cytotoxicity (CDCC)
- Identification of tumor specific membrane receptor antigens
- Monoclonal antibodies for diagnosis and therapy

**Strategy for research and development:**

1. Biopsies
   - Tumoral Normal tissue
   - Two-dimensional gel analysis
2. Protein analysis
3. Mass spectrometry
   - Tumor specific protein spots sequencing
4. Monoclonal antibodies
   - Development of Mab mediating tumor cells cytotoxicity

**Ongoing connection:**
with CGE investigators (Besançon, Dijon, Nancy, Strasbourg)
OncoTrans meetings

- Bi-yearly meeting
- Invitation of lecturers from collaborating centers in France and in neighbouring countries
- 9 sessions covering all aspects of translational research
- Focus on functional molecular imaging
Core Thematic C
Viral Infection and Cancer

Pr Christine CLAVEL
(Inserm UMRS-903 and Pol Bouin Laboratory, University Hospital, Reims)
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)**

- **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
Other tumor viruses: EBV and HCV

Epstein-Barr and cellular microRNAs variations in post-transplantation lymphoproliferative 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 paroviruses infection (Heidelberg and Strasbourg)
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
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
## 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*

#### 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*
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 ?
**Parvovirus**

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

**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
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.)
Carcinogenesis

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

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

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)
**Hepatitis C Virus (HCV)**

**HCV entry: therapy for hepatocellular carcinoma?**

**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

![Model of HCV entry in a human hepatocyte (Baumert et al.)](image)

**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.)
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 disparities with regard to cancer

- **Tools**:  
  - Cytology arm (women 25-30 years)  
  - HPV arm (women 31-65 years)
Broadening of the alliance with DKFZ

- Tumor Virology: part of the broadened collaboration

Concertation with regional governments

- Strengthening of the Champagne-Ardenne Hospital Biology Platform
- Acquisition of siRNA libraries (druggable genome, ...), contribution to deep sequencing cost
- Strengthening 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
Core Thematic D

Cancer Functional Omics

2 major workpackages
Genome/Epigenome/Transcriptome
Tumor microenvironment

2 coordinating research institutions
IGBMC (Strasbourg) *Dr Cécile ROCHELLE-EGLY*
IFR53 (Reims) *Pr Philippe BIREMBAUT*
In continuity of former « Axis 4 »
« Control of tumor dissemination »
Coordinated by MC Rio (IGBMC)

Funding of 27 projects, 49 teams

Creation of the« Transfected Cell Array » platform
renamed to
« High-Throughput Cell-based Screening platform »

Extensions and integration of new model systems
Cancer cell

Aberrant epigenetic modifications
DNA
Histones
Transcription factors

Aberrant Kinome

Aberrant gene expression
Transcriptome

Aberrant proliferation/invasion

Genome
DNA damage
DNA repair
Objective

Implement integrated approaches to:

Improve knowledge in genome, epigenome, transcriptome alterations and in tumor progression

Identify novel therapeutic targets and innovative biomarkers

Characterize drug candidates
Assets of the program

Critical mass of researchers

High-throughput technologies

*In vitro and in vivo* functional assays
Coordination driven by

Leading research center devoted to the study of gene expression in human diseases and cancers

Expertise in tumor progression and in tumor microenvironment
Genomic alterations in cancer

Visualisation of DNA Breaks
Genes involved in translocations

Characterisation of genes/factors involved in repair
Epigenetic alterations
Phosphorylation/Methylation/Acetylation/Ubiquitination

Transcription Factors

Histones

DNA

Cell reprogramming

Gene transcription
mRNA, microRNAs

Silencing of tumor suppressors
Overexpression of oncogenes
- Cancer Functional Omics -

- Tumor cell proliferation
- Extracellular matrix molecules
- Proteases
- Matrikines

- Tumor invasion
- Epithelial/mesenchymal transition
- Stroma

- Angiogenesis

- Metastasis
Genome-wide techniques and Bioinformatic tools

**IBISA platforms and core facilities**

**High-throughput RNAi based screens** (High-throughput cell-based phenotyping platform)

**High-throughput gene expression**
Microarrays and deep sequencing platform (ChIP-seq, RNA-seq)

**Protein networks and protein modifications analysis**
Mass spectrometry, electronic microscopy, structural biology platform

**Dynamic and structural changes** (NMR, biocomputing)

**Nuclear organisation and dynamics** (Imaging platform)

**Analysis of the affected genomic regions** (ChIP-seq)

**Cell culture and animal facilities**
Microspectral techniques for cell and tissue imaging

Images obtained by infrared spectroscopy after multivariated statistic treatment of the spectra (regroupment of spectra by clusters, each cluster is represented by a color)

This representation allows to identify the different tissue compartments on the basis of specific spectral signatures

The analysis of these spectral signatures allows to access to molecular informations present in the vibration spectra.

This approach may have clinical applications for identifying the tumor margins and biological applications for understanding the tumor microenvironment interactions.
Cellular models
Xenografts
Samples from tumor banks

High level technological platforms

Strong interactions between biologists and clinicians

Define promising candidates
For diagnosis and prognosis

Mechanisms of therapeutic resistance

Therapeutic applications
New pharmacological agents
Contribution to Plan Cancer II
Involvement in EU programmes

**COLCATS (new druggable targets for the treatment for the colorectal cancer) - EuroTransBio**
- **IGBMC Researcher**: Laurent BRINO
- **Project Coordinator**: Loïc CERF, FLUOFARMA (France)
- **Participating teams**: 3 teams from France and Germany

**EuTRACC (European Transcriptome, Regulome & Cellular Commitment Consortium) - FP6**
- **IGBMC Researcher**: Laszlo TORA
- **Project Coordinator**: Frank GROSVELD, Erasmus University Medical Center, Rotterdam (The Netherlands)
- **Participating teams**: 20 research groups from 9 different countries

**CANCER DEGRADOME - FP6**
- **IGBMC Researcher**: Marie-Christine RIO
- **Project Coordinator**: Dylan EDWARDS, University of East Anglia, Norwich (United Kingdom)
- **Participating teams**: 41 scientists from 28 academic and 5 SME teams (13 countries)

**EPITRON (EPIgenetic TReatment Of Neoplastic disease) - FP6**
- **IGBMC Researcher**: Hinrich GRONEMEYER, IGBMC (Strasbourg) - **Project Coordinator**
- **Participating teams**: 14 members (10 research groups, 3 SMEs and 1 big pharma) from 7 different countries

**PRIMA Project (PRostate cancer Integral Management Approach) - FP6**
- **IGBMC Researcher**: Bohdan WASYLYK, IGBMC (Strasbourg)
- **Project Coordinator**: Pr Jack SCHALKEN, University Medical Center, Nijmegen (The Netherlands)
- **Participating teams**: 16 participants from 8 different countries
Perspectives

New deregulated molecules or landscapes

New therapeutic avenues (specific targeting or reprogramming approaches)
CGE Actions

Networking

International partnerships

Technology development (proteomics equipment and staff)

Support scientific international meetings (Retinoid meeting, September 2011, Illkirch)
Core Thematic E
Molecular and Cellular Immune Therapies of Cancer

Dr Olivier ADOTEVI (University Hospital – Inserm UMR 645 – French Blood Agency, Besançon)

Dr François Ghiringhelli (Anti-cancer center– Inserm avenir team–, Dijon)

Dr Eric Robinet (Inserm U728, Strasbourg)

Dr Christian GARBAR (Institut Jean Godinot (Fnclcc) , Reims)

Pr Sylviane Muller (CNRS UPR9021 IBMC Strasbourg)

Pr Christophe BORG (University Hospital – Inserm UMR 645 – French Blood Agency, Besançon)
**Immunity and Cancer Organizational Chart 2011-2014**

- **Peptides or small molecules**
  - Monoclonal antibodies
  - Gene and Cell engineering
  - Vaccination

- **Peptides or chemical compounds**
  - Monoclonal antibodies
  - T-bodies; T lymphocyte reprogramming
  - Therapeutic viruses
  - A2/DR1 Tg mice

- **Pharmacology, B Royer**
  - Drug screening, D Rognan
  - Chemical synthesis, Marc Pudlo
  - Peptide biology, C Müller
  - Pathology, C Garbar, Reims CLCC

- **mAb, C Borg**
  - Phage display, Y Godet/J Balland
  - Proteomic: IFR 85, JR Pallandre/W Boireau

- **Gene therapy, C Ferrand**
  - Cell Therapy, C Borg/M Deschamps

- **PithCell**
  - A national platform for cellular manufacturing

- **Ag discovery, O Adotevi / Y Godet**
  - Immunomodulation, F Ghiringhelli

- **Cytheris**

- **Basic research**
  - Biotechnological development
  - Preclinical studies
  - Clinical trial design and promotion
  - Innovation
  - Proof of concept
  - Cocolin

- **Industrial partnership**

**Immunity and Cancer Objectives**

**Mission 1:** develop clinical approaches to modulate Host-graft and cancer interactions

**Mission 2:** identify and study critical signaling pathways involved in Host-Graft-Cancer regulation.
Immunity and Cancer Presentation

Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies

C Borg, M Deschamps/UMR 645 INSERM
E Robinet/U728 INSERM
E Deconinck CIC-BT506

Transgene (oncolytic viruses)
Miotheris (locoregional therapies)
EFS and LFB (cell therapy platform)
(PithCell Project/«Investissements d’Avenir»)

Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development

O Adotevi, C Borg/UMR 645 INSERM
F Ghiringhelli, Avenir INSERM
S Müller/S Fournel, CNRS UPR9021 IBMC
C Garbar, pathology-Reims CLCC
Invectys (DNA Vaccination)
Cytheris (GMP Cytokines)
ITAC Platform/Diaclone and Transgene (Antibodies)
Immugene and neoMPS (GMP peptides)

Investigating the signaling pathways that modulate host-tumor-graft interactions

Immune targeting of cancer cells using alternative splicing or resistance-associated molecules as a source of tumor associated antigens.

C Ferrand and B Royer/UMR 645 INSERM

Graft

Lymphocytes T
Lymphocytes NK
Mesenchymal stem cells

Patient

Tumor

HvG
HvG prevention
GvH
GvL

Immunity and Cancer Presentation

Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies

- NK cell therapy (PHRC INCA/phase I)
- Lymphocyte genetic reprogramming (PHRC/phase II)
- Deschamps M et al Blood 2007
- Letondal P et al Hum Gene Ther 2008
- Bennour E et al Hum Gene Ther 2007
- Deschamps M et al. Mol Immunol 2007
- Patent TK optimisation licenced/Molmed

Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development

- Al-Jamal, K. T. et al PNAS 2010
- El Khoury, D et al BMC Cancer 2010
- Royer B et al. Br J Cancer 2010
- Adotevi O et al Blood 2010 (patent and collaboration with Invectys)
- GrandClement C et al Plos One in revision and
- Patent 08/04725 (development ITAC platform and transgene)

Immune targeting of cancer cells using alternative splicing or resistance-associated molecules as a source of tumor associated antigens.

- Henry et al Blood 2010 patent 08.06444

Investigating the signaling pathways that modulate host-tumor-graft interactions

- Deschaseaux F et al Stem cells 2007
- Pallandre et al Exp Hematol 2007
- Palandre et al JI 2007
- Pallandre JR et al Blood 2008
- Bedel R et al Cancer Res 2011
- Monnien F et al J Clin Pathol 2010
**Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies**

**Immune targeting of cancer cells using alternative splicing or resistance-associated molecules as a source of tumor associated antigens.**

**Immune Targeting of Cancer**

Vaccination, small molecule, peptide and monoclonal antibody development

**Investigating the signaling pathways that modulate host-tumor-graft interactions**
Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies

- Lymphocytes T
- Lymphocytes NK
- Mesenchymal stem cells

Donor T cell expressing
HStk and NeoR genes

Allogeneic NK cells
Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies

Suicide gene Therapy to control Graft-versus-Host disease in Allogenic HSCT

12 patients with high risk of GvH disease

4 patients treated and in life 10 years after gene therapy

1. Demonstration of the presence of TK+ lymphocytes 10 year following T cell adoptive transfer
2. An alternative splicing of TK leading to a non functional protein occurred.
3. Correction of the alternative splicing sites: patent 0008966.4 (Blood 2007)
4. Licensing to Molmed, generation of a new phase II clinical trial: 2010
**Immunity and Cancer**

**Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies**

**Phase I clinical trial: Allogenic Natural Killer lymphocytes and cetuximab in EGFR+ gastro-intestinal adenocarcinoma**

**Phase I clinical trial : treatment of liver metastases of EGFR+ gastro-intestinal cancers.**

→ Allogeneic NK GMP production

→ Lympho-depleting regimen based on fludarabine and cyclophosphamide

→ adoptive transfer into the liver artery

→ association of ADCC and NK alloreactivity (cetuximab treatment)
**Objective:**

To promote interactions between CGE research teams to enhance our basic knowledge and innovation in cancer immunology.

**Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies**

- Graft
- Lymphocytes T
- Lymphocytes NK
- Mesenchymal stem cells

**Immune targeting of cancer cells using alternative splicing or resistance-associated molecules as a source of tumor associated antigens.**

- Patient
- Graft
- HVG
- HVG prevention
- GvH
- GvL

**Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development**

**Investigating the signaling pathways that modulate host-tumor-graft interactions**
Investigating the signaling pathways that modulate host-tumor-graft interactions

CX3CR1

Pallandre JR et al Blood 2008

Biomonitoring platform

T280M (+839C>T)

Kidney transplanted patients: Didier Ducloux: 603 patients Biomonitoring Plateform, Philippe Saas

In multivariate analysis, patients displaying a TT genotype have an enhanced incidence of cancer (Hazard ratio (HR) 3.53 [95% CI 1.35-9.28], p=0.010).

CIC-BT506

MDSC: Myeloid Derived Suppressive cells; DC: Dendritic cells; NK: Natural Killer Cells


Immunosuppression

1. Vincent J et al Cancer Res 2010
2. Chalmin F Journal of Clinical Investigation 2010
Immunity and Cancer: Project

Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies

Immune targeting of cancer cells using alternative splicing or resistance-associated molecules as a source of tumor associated antigens.

Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development

Investigating the signaling pathways that modulate host-tumor-graft interactions
Identification of an alternative RNA expressed in B cell lymphoma: a new LNH-associated antigen?

**A.** A specific alternative splicing of CD20 (ΔCD20) was identified in B cell lymphoma resistant to Rituximab

**B.** In vivo stimulation of HLA-A2 DR1 Transgenic mice with RMS peptides

**A predictive approach** was used to identify specific peptides associated with ΔCD20

<table>
<thead>
<tr>
<th>Peptide N°1:</th>
<th>LFRMSSL/E</th>
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<tr>
<td>Peptide N°2:</td>
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<tr>
<td>Peptide N°7:</td>
<td>SL/ELVIAGI</td>
</tr>
<tr>
<td>Peptide N°8:</td>
<td>L/ELVIAGIV</td>
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</table>

Blood 2010 patent 08.06444
Immunity and Cancer: Project

Cell and gene engineering to modulate allo-immune responses and Chemo-immunotherapies

Immune targeting of cancer cells using alternative splicing or resistance-associated molecules as a source of tumor associated antigens.

Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development

Investigating the signaling pathways that modulate host-tumor-raft interactions
Immunity and Cancer: Project

A. Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development

B. Adotevi O et al Blood 2010:
Identification of hTERT derived T CD4 peptides

C. TERT CD4 peptides enhance anti-TERTp988 CD8 T cell response

D. Invasion

Cytheris

Immunity and Cancer: Project

Immune Targeting of Cancer Vaccination, small molecule, peptide and monoclonal antibody development

Nucleoline ligand/nucleophosmine is expressed on tumoral and endothelial cells

A. Peptide N6L

B. Control N6L

C. Control N6L 10 µM N6L 50 µM N6L 100 µM

D. Fluorescent N6L distribution

E. MDA-231 xenograft

Fluorescent N6L distribution

MDA Mb 231

U87MG

CNRS UPR9021 IBMC Strasbourg
Immunity and Cancer: Project

**Immune Targeting of Cancer**

Vaccination, small molecule, peptide and monoclonal antibody development

---

**A.**

Immunological targeting of cancer

**B.**

Non-malignant human colonic mucosa  
Colonic adenocarcinoma

**C.**

Colo320-shRNA-ctrl  
Colo320-shRNA-NRP2

---

**D.**

HT29

**E.**

Medium  
TGF-β1  
Smad 2/3

**F.**

P-Smad 2

---

Immunity and Cancer 2011-2014

- Peptides or chemical compounds
- STAT3 inhibitors
- Monoclonal antibodies
- NRP2-mAb
- Cooper antibodies
- T-cell reprogramming
- CD20 peptide vaccination
- ΔCD20 peptide vaccination
- CD4-hTert DNA vaccination
- IL-7 treatment
- A2/DR1 Tg mice
- T-bodies; T lymphocyte reprogramming
- Peptides or small molecules
- Gene and Cell engineering
- Vaccination
- Basic research
- Biotechnological development
- Preclinical studies
- Clinical trial design and promotion
- Innovation
- Proof of concept
- Industrial partnership
Eastern-France Canceropole and the Plan Cancer II

2011-2014 Provisional Budget and Funding Requirements

Pr. Pierre OUDET
Scientific Director
### 2011-2014 budget

#### Global financial request:

<table>
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<th>TOTAL (KC)</th>
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<td>INCa</td>
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<tr>
<td>Membership fees</td>
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<tr>
<td>Partnerships (Caisse d’Epargne)</td>
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<td>Sponsoring</td>
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#### Coordination activities:

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<th>Events</th>
<th>Training</th>
<th>Staff</th>
<th>Running cost</th>
<th><strong>TOTAL (KC)</strong></th>
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<tr>
<td><strong>TOTAL</strong></td>
<td>246</td>
<td>46</td>
<td>1,140</td>
<td>360</td>
<td>1,792</td>
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#### Core Thematics:

<table>
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<th>Staff</th>
<th>Equipment</th>
<th><strong>TOTAL (KC)</strong></th>
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</thead>
<tbody>
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<td>385.0</td>
<td>472.5</td>
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<td>Translational Research (B)</td>
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<td>43.8</td>
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<td>Infection &amp; Cancer (C)</td>
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<td>Functional –Omics (D)</td>
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<td>17.5</td>
<td>157.5</td>
<td>390.3</td>
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<tr>
<td>Immunity (E)</td>
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<td>17.5</td>
<td>105.0</td>
<td>122.5</td>
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<td><strong>TOTAL (KC)</strong></td>
<td><strong>133.8</strong></td>
<td><strong>1,268.7</strong></td>
<td><strong>387.3</strong></td>
<td><strong>1,789.8</strong></td>
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### Anchoring within Plan Cancer

#### CGE & Plan Cancer II:

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<th>Category</th>
<th>Amount (K€)</th>
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<td>Disparities &amp; Cancer</td>
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<td>Integrated Research</td>
<td>767.1</td>
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<td>Platforms* (incl. dedicated personnel)</td>
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<td>Training for and by research</td>
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<td>Dedicated information towards diverse populations</td>
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<td><strong>TOTAL (K€)</strong></td>
<td><strong>2 099.4</strong></td>
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</tbody>
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* QoL, Histopathology, Proteomics, Xenografts
Towards Translational Research aiming Personalized Oncology