Welcome from Institut Gustave Roussy

Professor Eggermont, The Director General - Institut Gustave Roussy
Gilles Bloch, President - Université Paris-Saclay
Professor Vassal, Professor of Oncology - University Paris-Sud
Precision Cancer Medicine and Big Data with a focus on children with cancer

Gilles Vassal
Each human being is unique
Desoxyribonucleic acid, DNA
4 bases

1 human genome = 3 x 10⁹ basepairs

25,000 to 30,000 genes
DNA sequencing of the First Human Genome
Started 1990
13 years, $2.7 bn
Completed on April 14, 2013
Sources: National Human Genome Research Institute and author's calculations.
Genetic ancestry test

Genetic paternity test

Genetic compatibility test

Genetic fingerprinting

Personalized medicine

Genetic disease risk
Cancer

• Interaction between Genome and Environment
  – Eg, Tobacco, UV, virus,........
  – Somatic alterations

• Genetic predisposition
  – Eg Breast cancer (BRCA)
  – Constitutional DNA
Cancer
Normal Lung

Lung cancer
Cancer
Molecular alterations
Heterogeneity

Immune system
Proteins
Genes
definition of cancer

A definition from the XXth century

Significantly mutated pathways in adenocarcinoma of the lung

Ding et al. Nature 455, 1069, 2008

A definition from the XIXth century

a tumor

an organ

a pathological sample

= [Diagram showing significantly mutated pathways in adenocarcinoma of the lung]

Ding et al. Nature 455, 1069, 2008
Lung Cancer Molecular Subtypes
Cancer signaling is not linear.... It is a highly interconnected and redundant network...
Development of oral crizotinib, ALK MET inhibitor

Enrichment of phase 1 with EMLA4-ALK patients
RR = 1CR + 46PR/82 (57%) with a PFS at 6 months = 72%
EML4-ALK fusion gene = 2 to 7% of NSCLC
Specific genetic traits can predict for the success of targeted agents

Recent examples of oncogenic addiction in solid tumors leading to active inhibitors - i.e. “superstars”!

**B-RAF inhibitor in melanoma (V600E BRAF mutation) NEJM 2010**
- vemurafenib

**Hedgehog inhibitor in BCC (PTCH mutation) NEJM 2010**
- vismodegib

**ALK inhibitor in NSCLC (ALK translocation) NEJM 2010**
- crizotinib

Phase I data; all drugs are registered
Which drug(s) for Mister X?

Tailored medicine

Challenge
To prescribe the right drug combination
At the right time

Precision Medicine
A public health and societal issue
To Increase survival using expansive drugs only for patients who will benefit

Drugs/biomarker

Algorithms for decision making
Precision cancer medicine

At least for a first step: Stratified Medicine

1. Moving away from empirism and serendipity to a biology-based therapy

2. Matching the right drug with the right cancer type

3. Defining the right response biomarker on each patient’s tumor

4. Organizing molecular follow up of patients under therapy

The Ultimate goal
individual biology-guided treatment decision
MOLECULAR SCREENING*

CGH Array & NGS
WES, RNAseq

CLINICAL DECISION
TREATMENT

FRESH TUMOR → MOLECULAR SCREENING* → CLINICAL DECISION → TREATMENT

Max <21 calendar days

*From 15 genes to 25000 genes In 4 years
Per tumor sample

Antoine Hollebecque et al., ASCO 2013; Charles Ferte et al, AACR 2014

• Monocentric
• 1200 patients – 2011-2015
105 actionable aberrations used to choose the targeted treatment

27 most frequent abnormalities represent 78% of the actionable aberrations

Actionable aberrations used to chosen the targeted treatment

- Amplification
- Mutation
- Translocation
- Deletion
- Loss

Frequency (N)
Figure 1. Patient I Clinical Course Including Treatment History and Relevant Imaging Studies and Tumor Biopsy Specimens

Legend:
- ▲ Biopsy
- □ Irradiation

BSI: brain stereotactic irradiation; LCI: lung conformational irradiation; FI: Femoral irradiation; SC: scapula irradiation

Epidemiology

EGFR Del19 and T790M positive

Gefitinib

AZD9291

CDDP PEM
Applications of Liquid Biopsy

Monitoring & Early Detection

- Brain cancer DNA blocked by blood-brain barrier

Detection of Resistance Mutations

- Targeted therapy
- Response to therapy
- Selective pressure
- Resistance mutations

Multiple Tumor Types

- Breast cancer
- Pancreatic cancer
- Colon cancer

Many tumors release DNA fragments that circulate in the bloodstream

ctDNA & Tumor Cell Analysis

- ctDNA
- ctDNA of resistance mutations collected in blood sample

Courtesy A Bardelli
Cancer in Young People in Europe

- Each year: 35,000 new cases
  - 15,000 <15 years and 20,000 15-24 years

- 80% are disease-free at 5 years with multidisciplinary treatments
  - 300,000 EU citizens are childhood cancer survivors
  - 2/3 have long-term side-effects

- 6,000 young people die each year

Cancer: first cause of death by disease beyond one year in EU

STILL A PUBLIC HEALTH ISSUE
Pediatric malignancies are different from malignancies in adults
THE SIOPE STRATEGIC PLAN
A European Cancer Plan for Children and Adolescents

http://www.siope.eu/SIOPE_StrategicPlan2015/
By 2025:

- To increase cure rate in patients with poor prognosis malignancies
- To increase quality of life (cure) in survivors
- To tackle inequalities

A long term sustainable strategy

Designed within the FP7
Created in 2003, ITCC is a consortium of 49 institutions in 12 countries

ITCC runs a comprehensive clinical and biological early evaluation program of anticancer drugs for children and adolescents.

Each year, 4,500 patients with cancer are diagnosed in ITCC centers.

20% of them experience recurrence of their disease and are offered to participate in ITCC trials.
MOSCATO-01 (pediatric cohort)

- 78 patients included; Data from 60 with results from 65 interventions
  - 62% solid tumors; 38% CNS tumors
  - Median age: 11.1 years (range, 0.8-24.3y)
- 56/60 patients had a molecular analysis done
- 32 of 56 (57%) had at least 1 actionable target
Bioinformatics of Precision Cancer Medicine

Speed and storage are essential!

• Raw data for one sample and calculation = 300 Go
• One patient = Tumor + constitutional DNA
• quality control+mapping+variant calling+annotation
• DELL Cluster* (since 215) [servers + storage+network]
  – 96 samples in parallel per day versus 12 per day
• Acceleration = x11
• 1000 patients = 600 To duplicated = 1,2 Po

*dedicated to the pediatric programm
The Innovative Therapies & PCM Programme

1. A tumour molecular profile* for patients at relapse
   *WES, RNAseq, Immununo
   Molecular Matching Trials

2. New targeted and immune therapy drugs
   Trials w single agents and combinations

SHARE

With ECTGs

EU Clinico Biological Database

Paediatric New Drug Development

New knowledge, targets, pathways
1. Generate molecular profiling for each patient

2. MATCH

3. Evaluate drugs and combinations

Phase 1 & 2 ITCC Trials
(sponsored by industry and ISTs)

MATRIX trial (Genentech/Roche)
(2 drugs – atezolizumab; cobimetinib)

4. Create

European clinico-biological database

5. New knowledge

new druggable pathways for specific pediatric drug development

INFORM (Germany)

MAPPYACTS (France, Spain, Denmark, Italy)
nITHER (Netherlands)

S-PED (UK)

WES, RNA seq, methylome immunophenotype

1000 children and adolescents 4 years

1000 children and adolescents 4 years

1000 children and adolescents 4 years
Projet National MAPPYACTS

MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification

Enfant et adolescent, en rechute, tumeur solide et leucémie

Biopsie à la rechute → Portrait Moléculaire Tumoral (WES/RNAseq) → RCP moléculaire → Traitement

300 enfants en 3 ans
PHRC 2015
Fondation ARC
Ouverture décembre 2015
Children and their parents need to travel to investigating centers to access early innovation
A multistakeholder platform
(Academia, Parents, Industry, Regulatory)

Vassal, Eur J Cancer, 2015, 51, 218
Accelerating Understanding Summit 2016
31 May - 1 June 2016, Paris, France
Thanks to the patients and their family

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ANR

MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ

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Imagine d’Enfants

Dell

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