Paris, May 9, 2012

**Press release**

# Liver cancer: The first high-speed sequencing results obtained in France.

**Since 2009, France has been running a major pilot clinical trial into liver cancer as part of the International Cancer Genome Consortium (ICGC) project. The aim of this project is to sequence the genomes of the tumors from several thousands of patients suffering from around fifty different cancers, in order to gain a better understanding of the part played by genetic alterations in the development of these cancers. The work carried out by Jessica Zucman-Rossi's team (Inserm unit 674 "Functional genomics of solid tumors" working jointly with the Université Paris Descartes), revealed 4 genes that had never been described in liver tumors, even although they presented frequent alterations. These genes, identified as *ARID1A*, *RPS6KA3, IRF2* and *NFE2L2,* are involved in important processes that lead to the development of tumors in the liver. This research was published in the May 6, 2012 issue of *Nature Genetics*.**

**The work done by the French teams is coordinated by the INCa and Inserm. It includes 4 programs that each study a particular type of breast cancer, aggressive prostate cancers, Ewing's sarcoma and liver cancer.**

Liver cancer is the third most frequent cause of death in the world. It often occurs in persons whose liver is already affected by pathologies such as hepatitis B or C, excessive alcohol consumption, iron overload or obesity. These pathologies can lead to the development of cirrhosis of the liver.

In France, a pilot study was initiated in 2009 on a first series of 24 hepatocellular carcinomas within the framework of the ICGC sequencing consortium. The aim of this study led by Jessica Zucman-Rossi was to find new genes responsible for the development of liver tumors (tumor suppressor genes and/or oncongenic genes).

Using new genome sequencing techniques, the researchers were able to establish that the genetic code[1] of persons suffering from liver cancer often presented modifications, in which the G bases had been replaced by T bases. These mutations seem to be specific to and closely linked to liver cancers. This strongly suggests that, where there is no previous cirrhosis of the liver, a toxic agent is involved in the process and causes mutations in the DNA of these patients.

In tropical areas, compounds such as aflatoxin B1[2] are already well known for similar cancer-producing effects. New epidemiological and toxicological data will be needed to accurately determine what kind of genotoxic agents can affect patients living in France.

---

1 based on the four ATCG bases

2 **Aflatoxine** is a toxin that is secreted by a fungus(*Ascomycete aspergillus flavus*) that exists in large quantities on different seeds in hot, wet, conditions. It is a powerful oncogenic agent, affecting the liver in particular, and is also an ARNm sythesis inhibitor.

**Identification of 4 new genes involved in liver tumors**

An analysis of all the observed mutations brought to light four new genes that had never before been described in hepatic tumors, and yet they present recurrent genetic alterations: *ARID1A, RPS6KA3, IRF2* and *NFE2L2.* In order to understand what part they play, these four genes were tested along with the 10 other genes, on samples from 125 hepatic tumors.

From a physiological point of view, it seems that certain of these genetic mutations seem to alter two signaling pathways known to the scientists: The WNT/p-Catenine pathway and the P53 pathway.

Others on the other hand, are involved in triggering off oxidative stress, interferon or RAS signaling, thereby disturbing the state of the cells.

Finally, in patients suffering from chronic alcohol intoxication, the chromosome remodeling genes (that stabilize DNA) are often altered, making them major factors that contribute to hepatic tumor genesis.

As far as Jessica Zucman-Rossi is concerned, “This study reveals new tumor-suppressor and oncogenic genes involved in hepatic carcinogenesis. New lines of investigation are still to be explored so that the future will see new medication that is able to target the genetic alteration and thus improve and tailor the treatment of the patients to treat the genome abnormalities identified in their tumors.”

This work was coordinated and financed by the INCa as part of the Cancer Plan 2009-2013, in close collaboration with the Ligue nationale contre le cancer and Inserm.

## The Institut national du cancer – The French partner of the internal ICGC consortium

*The International Cancer Genome Consortium* (ICGC) is a global program of high-level biomedical research. It is one of the most ambitious programs since the Human Genome project (http://www.icgc.org/). Launched in 2008, the ICGC program, that currently involves 14 countries, has the task of drawing up a complete description of the genomic, transcriptomic and epigenomic alterations of 50 cancer types or subtypes considered to be the most preoccupying both from clinical and society points of view.

25 000 cancer genomes are to be sequenced and analyzed and the results will gradually be entered into a database that will be accessible to researchers the world over. The list of genomic alterations specific to each type of cancer will enable us to develop functional investigations on the mechanisms of carcinogenesis, and will provide new strategies for prevention, diagnosis and treatment.

The member organizations and the research centers taking part in the ICGC have agreed to abide by standards governing informed consent and common ethical rules, in order to ensure that the identity of each participant is protected.

The Institut national du cancer (INCa) has overall coordination of the French contribution to this program. It benefits from financing by INCa and Inserm amounting to 5 M € per year.

The ICGC program is an opportunity to consolidate the organized effort undertaken by the INCa in the field of high-level genomics.

In 2012 INCa and Inserm took on 4 projects concerning liver cancer, HER2+ breast cancer, prostate cancer and Ewing’s sarcoma. A fifth program is to be started in 2012-2013

**Sources**

**Integrated analysis of somatic mutations and focal copy number changes identifies key genes and pathways in hepatocellular carcinoma**

Cécile Guichard1,2*, Giuliana Amaddeo1,2*, Sandrine Imbeaud1,2*, Yannick Ladeiro1,2, Laura Pelletier1,2, Ichrafe Ben Maad1,2, Julien Calderaro1,2,3, Paulette Bioulac- Sage4,5, Mélanie Letexier6, Françoise Degos7, Bruno Clément8, Charles Balabaud4,5, Eric Chevet4, Alexis Laurent9,10, Gabrielle Couchy1,2, Eric Letouzé11, Fabien Calvo12, Jessica Zucman-Rossi1,2,13**.

1 Inserm, UMR—674, Génomique fonctionnelle des tumeurs solides, IUH, Paris,F—75010 France
2 Université Paris Descartes, Labex Immuno—oncology, Sorbonne Paris Cité, Faculté de Médecine, Paris, France
3 Assistance Publique—Hôpitaux de Paris, Department of Pathology, CHU Henri Mondor, F—94000 Créteil, France
4 Inserm, UMR—1053; Université Victor Segalen Bordeaux 2, Bordeaux, F-33076, France
5 CHU de Bordeaux, Pellegrin Hospital, Department of Pathology, Bordeaux, F—33076, France
6 IntegraGen, F—9100 Evry, France
7 Assistance Publique—Hôpitaux de Paris, Department of Hepatology, Beaujon Hospital, Université Paris Diderot, F—92210 Clichy, France
8 Inserm UMR—991, Université de Rennes 1, F—35043 Rennes, France
9 Assistance Publique—Hôpitaux de Paris, digestive, hepatobiliary and liver transplantation, CHU Henri Mondor, F—94000 Créteil, France
10 Inserm, U955, F—94000 Créteil, France
11 Programme Cartes d'Identité desTumeurs, Ligue Nationale Contre le Cancer, F—75013 Paris, France
12 Institut National du Cancer, INCa, F—92513 Boulogne, France
13 Assistance Publique—Hôpitaux de Paris, Hopital Europeen Georges Pompidou, F—75015 Paris, France

***Nature Genetics,*** http://dx.doi.org/10.1038/ng.2256

**Research contact**

**Jessica Zucman-Rossi**
**Inserm 674 "Génomique fonctionnelle des tumeurs solides" joint research unit with the Université Paris Descartes**
Tel : 06 01 07 78 75
E-mail address: jessica.zucman-rossi@inserm.fr

**Press Contact**

presse@inserm.fr