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PRESS RELEASE

Metastatic melanoma

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NEW RESISTANCE MECHANISMS TO MELANOMA TARGETED THERAPIES: CONTRIBUTION OF THE TRANSLATION OF RNAs INTO PROTEINS

French investigators have discovered new resistance mechanisms to targeted therapies used for less than three years in the treatment of melanoma. This discovery enables us not only to better understand why these treatments become ineffective but also to reveal new avenues for the management of these aggressive tumours. These studies have been published in the review *Nature*¹ and have the benefit of an early on-line publication.

<http://www.nature.com/nature>

The treatment of metastatic melanoma remains a major problem in oncology. Half of the patients suffering from this disorder have a mutation of a protein called BRAF. Medicines targeting this mutated protein, vemurafenib (Zelboraf®) and dabrafenib (Tafinlar), enable the progression of this type of skin cancer to be significantly delayed. Unfortunately, over time, these anti-BRAF compounds lose their efficacy.

Investigators from the Predictive Biomarkers and new molecular strategies in anti-cancer therapy laboratory (Inserm/Gustave Roussy/Paris-Sud University) have shown that the mechanisms used by tumours to resist these treatments involves a protein complex called eIF4F which regulates the synthesis of proteins from RNA. From the biopsies of tumours from patients, investigators also showed that the formation of this complex was diminished in tumours which responded to anti-BRAF and was increased in resistant metastases.

¹ **eIF4F is a nexus of resistance to anti-BRAF and anti-MEK cancer therapies**, Lise Boussemart^{1,2,3*}, Hélène Malka-Mahieu^{1,2*}, Isabelle Girault^{1*}, Delphine Allard¹, Oskar Hemmingsson¹, Gorana Tomasic⁴, Marina Thomas³, Christine Basmadjian⁵, Nigel Ribeiro⁵, Frédéric Thuaud⁵, Christina Mateus³, Emilie Routier³, Nyam Kamsu-Kom¹, Sandrine Agoussi¹, Alexander M. Eggermont^{2,3}, Laurent De saubry⁵, Caroline Robert^{1,2,3} & Stéphan Vagner^{1,2,3}

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They have also shown that compounds developed by a pharmacology team of the CNRS and by the University of Strasbourg which inhibit the eIF4F complex bring about an improvement in the efficacy of vemurafenib in cellular and murine models.

These results offer new prospects for the prediction of the efficacy of melanoma treatments using medicines targeting the BRAF protein. Moreover, over the long term they may result in more effective new treatments emerging to treat not only this fearsome type of cancer, but also certain types of thyroid, colon, lung and brain cancers.

These studies have been conducted by Stéphan Vagner (Inserm U981/Gustave Roussy/Université Paris-Sud, Villejuif; Current address: CNRS UMR3348/Institut Curie, Orsay) and by **Caroline Robert** (Inserm U981/Gustave Roussy, Dermatology Department/Paris-Sud University, Villejuif) in collaboration with **Laurent Désaubry** (Therapeutic Innovation Laboratory, CNRS UMR 7200/University of Strasbourg, Illkirch).

The team of Drs Caroline Robert and Stéphan Vagner was supported by PAIR melanoma (Fondation ARC, The league Against Cancer and by INCa), Cancéropôle Ile de France and the group “Ensemble contre le mélanome” (Together against Cancer). This study has also benefited from the support of AAREC Filia Research, from the Wenner-Gren Foundation and from the Swedish Society of Medicine.

/ About Gustave Roussy

Gustave Roussy, a key centre in the fight against cancer in Europe, is a global skills hub against cancer completely dedicated to its patients.

It brings together on a single site, 2,630 professionals whose mandate is patient care, research and training.

Gustave Roussy in figures (in 2013): 356 beds and 89 day care places; 47,000 patients including 11,200 specialist consultants; 3,690 patients currently taking part in a clinical trial; 366 active on-going clinical studies; 321 patients in early phase I trials; 88 patients in early phase I/II trials – www.gustaveroussy.fr

/ About Inserm

Inserm, The National Institute for Health and Medical Research, has, for almost 40 years, been the only public French body dedicated to biological, medical and human health research with close to 15,000 researchers, engineers and technicians.

The Institute positions itself across the whole spectrum from research laboratory to the patient's bed and undertakes multidisciplinary research which enables the study of all illnesses from the commonest to the rarest. Inserm is the founding member of Aviesan*, the National Alliance for Life Sciences and Health created in 2009.

* Aviesan members: CEA, CNRS, CHRU, CPU, INRA, INRIA, INSERM, INSTITUT PASTEUR, IRD

Further information on www.inserm.fr

/ About the CNRS

Created in 1939, the National Centre for Scientific Research is a Public Research Body (Public Institution focussing on science and technology under the supervision of the Ministry of National Education, Higher Education and Research). It provides knowledge for the benefit of society. With close to 33,000 individuals, a presence over the whole of the country, CNRS is active in all fields of learning drawing upon 1,100 research and service units. With 19 Nobel prize laureates and 11 Fields Medals, the CNRS has a long tradition of excellence.

/ About the Paris-Sud University

The Paris-Sud University is a major player in the creation of the Paris-Saclay University which will open in 2014. Multidisciplinary and with a strong scientific and healthcare dominance, the excellence of its research is marked by numerous International prizes, notably in the field of mathematics (four Fields medals between 1994 and 2010) and of Physics (three Nobel prizes). The Paris-Sud University is one of the most prestigious Universities in Europe from the standpoint of research and is classified among the First French higher Education Institutions and 39th worldwide in the Shanghai 2013 classification.

The Paris-Sud University brings together more than 100 internationally renowned laboratories, takes in 27,600 students including 2,500 PhD students, it has 2,500 teacher-researchers and investigators and 2,700 engineers, technical and administrative personnel.

It has the largest campus in France with 2,700,000 m² of environmentally integrated heritage property in exceptional surroundings.

/ About the University of Strasbourg

European in disposition and with an International configuration, the University of Strasbourg was born on the 1st of January 2009 from the amalgamation of three Universities (Louis Pasteur, Marc Bloch and Robert Schuman). Created in the continuity of an ancestral tradition, it aims to promote transversality so that this interaction might give rise to new avenues of research and teaching meeting the needs of society. The International dimension is a fundamental characteristic of the University of Strasbourg; with extensive teams of investigators, reputed worldwide for their excellence and their efficacy, it has established itself among the chief European Universities in terms of research. Each of the principal fields of training of the University of Strasbourg relies on the Research Institutes, which represent the prime driving force of the Institution with more than 5,000 teachers and employees. The University of Strasbourg, takes in 44,000 students.

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