

## PRESS RELEASE

# A NEW PROGNOSTIC BIOMARKER FOR BREAST CANCER

***Scientists of the IFOM-IEO Campus have discovered a new “molecular circuitry” that regulates the protein p53. The finding, published today in the journal Nature, could find immediate clinical application as a prognostic biomarker. The therapeutic potential of this discovery is currently being investigated.***

Its name is NUMB and it can regulate p53, one of the proteins that plays a key role in the protection of genome integrity against potentially cancer-causing genetic damage. Without NUMB, p53 does not work properly, and the consequences of this are extremely severe: patient prognosis is less favorable, and tumors are more resistant to chemotherapy. The new mechanism involving NUMB was unveiled by a team of scientists from IFOM (IFOM, The FIRC Institute of Molecular Oncology Foundation), IEO (European Institute of Oncology) and the University of Milan, through a series of experiments performed on human breast cancer cells. The potential clinical applications are exciting. “With NUMB – says Pier Paolo Di Fiore, IFOM Scientific Director, Full Professor of General Pathology at the Medical School of the University of Milan and one of the two main authors of the study – we now have a new biomarker, ready to be used as a prognostic indicator for breast cancer. And, of equal, if not greater, clinical relevance, is a new ‘molecular circuitry’ that can be pharmacologically modulated in order to restore cells to normal.”

NUMB could already be employed as a prognostic biomarker in the clinic; all that is required is an evaluation of the quantity of NUMB in patient tissue samples. Giuseppe Viale, Director of the Division of Pathology at IEO, Full Professor of Pathological Anatomy at the University of Milan and co-author of the study, has already added this test to other routine clinical analyses already performed at IEO (the procedure involves immunohistochemical staining of standard histology samples that are ordinarily used for routine diagnoses). Pharmacological applications will require more time and experiments, although scientists remain optimistic. “We have devised – says IEO researcher Salvatore Pece, also Assistant Professor at the University of Milan and the second main author of the study – two possibilities for the therapeutic application of our findings. Both options now need to be tested in pre-clinical models and they could subsequently enter into clinical trials.”

The study, published today in the journal Nature, was made possible by support from the Italian Foundation for Cancer Research (FIRC, Fondazione Italiana per la Ricerca sul Cancro) and was funded by grants from the Italian Association for Cancer Research (AIRC, Associazione Italiana per la Ricerca sul Cancro) and MIUR to Salvatore Pece and Pier Paolo Di Fiore, from the European Community (VI Framework), The Ferrari Foundation, the Monzino Foundation and the CARIPLO Foundation to Pier Paolo Di Fiore, and from the G. Vollaro Foundation to Salvatore Pece.

### **Oncogenes and tumor suppressor genes**

The keywords we must define in order to better understand the significance of this finding are oncogenes and tumor suppressor genes. Tumor suppressor genes are proteins capable of protecting

cells from developing into cancer cells: they act as a form of “brake pedal” for cancer. One of the most important tumor suppressor genes is p53, which stops the cell cycle when genetic damage occurs, and allows cells to repair their damage before re-starting the cycle). Oncogenes are the exact opposite: they facilitate mechanisms, such as cell proliferation, that can trigger cancer degeneration. For this reason, oncogenes are often referred to as “accelerator pedals” for cancer.

Through a series of experiments carried out in cells isolated from human breast tumors, the team directed by Di Fiore and Pece have discovered and characterized the mechanism of interaction of the NUMB protein with the tumor suppressor, p53. They found that, when NUMB is present, it binds and protects p53 from degradation; as a result, p53 is maintained at levels that are high enough to protect the cell. In contrast, when NUMB is absent, another protein blocks p53 and targets it for destruction; as a result, cells lack protection against cancer.

The finding was confirmed by a genetic screen carried out on tissues from a cohort of 443 breast cancer patients who received adjuvant chemotherapy. The analysis showed that NUMB is absent or dramatically lacking in many of these tissues, and that NUMB absence tightly correlates with both a poor prognosis and with chemoresistance. “Loss of NUMB – explains Pece – leads to two severe consequences: on the one hand, it determines loss of the tumor suppressor p53, which means a loss of protection against cancer. On the other, lack of NUMB causes the level of another protein to increase: this protein is called NOTCH and it is a known oncogene.” With less tumor suppressor gene and more oncogene, cells start to proliferate without control.

### **Clinical applications**

“By using NUMB as a prognostic marker – says Pece – we can both better define the prognosis of breast cancer and also design more adequate pharmacological treatments.” Looking to the future, since the absence of NUMB determines both the inhibition of the tumor suppressor p53 and the increase of the oncogene NOTCH, drugs could be used that restore the balance, by both lowering oncogene activity and enhancing tumor suppressor activity. The idea, then, is to target upstream steps that modulate the whole NUMB-regulated process. “We would like to identify and characterize – says the first author of the study, Ivan Colaluca (IFOM, IEO) – the mechanism which is responsible for loss of NUMB in tumors. With this knowledge, one could think of pharmacologically restoring the level of NUMB and, so to speak, attack the root of the problem.”

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IFOM Press Office

Ph. +39 02 574303 042 / 206 – fax +39 02 574303041 – cell.: +39 339 1779787

e-mail: [team-press\[at\]ifom-ieo-campus.it](mailto:team-press[at]ifom-ieo-campus.it)

IEO Press Office

Ph. +39 02 89075034 / 02 57489013 – cell.: +39 335 6150331

e-mail: [dfrancese\[at\]consulenti-associati.it](mailto:dfrancese[at]consulenti-associati.it) – [ufficio.stampa\[at\]ieo.it](mailto:ufficio.stampa[at]ieo.it)