**DOMOTICS FOR CANCER: ANTISENSE MOLECULES**

**THAT TARGET TUMOR CELLS WITH PRECISION**

**From IFOM laboratories in Milan comes an innovative approach to fight tumors, analogous to domotics: it utilizes a class of antisense molecules that can selectively turn off the cellular systems responsible for signaling and repairing damage to the genome only where it is needed in cancer cells, just as a domotics system controls any light switch in a house independently. This approach could effectively impair cancer cell survival. The study, published in *Nature Cell Biology* and supported by AIRC and a prestigious ERC grant, lays the foundation for promoting therapies based on personalized medicine.**

Milan, November 27, 2017 – Tumor cells are characterized by genomic instability: their genome is constantly being broken, accumulating damage that the cell itself tries frantically to repair in order to survive and proliferate. It is becoming increasingly clear that identifying strategies to block DNA repair mechanisms and consequently eliminate tumor cells is a fundamental goal for treating cancer. The research team conducted by Fabrizio d'Adda di Fagagna, a researcher at IFOM in Milan and at the Molecular Genetics Institute of the National Research Council in Pavia, had already shown in a 2012 publication in *Nature* that some non-coding RNAs, that is, RNAs not translated into proteins, perform a crucial role as DNA guardians: whenever the DNA is damaged, they intervene by triggering an alarm that protects genome integrity. Research published today in *Nature Cell Biology* on the formation of these RNAs and how they function has led to a better understanding of how DNA damage is signaled and repaired, and hence to the development of solutions for blocking these mechanisms.

Working on human and mouse cells, the researchers have discovered a previously unreported scenario that could lead to effective and concrete therapeutic solutions. "Until now – explains d’Adda di Fagagna – it was believed that only proteins (ATM, ATR, PARP among the best known) were involved in DNA repair. Therapeutic approaches currently in use that target such protein factors are remarkably efficacious, but at the same time cause indiscriminate inhibition of DNA repair throughout the genome and thus have potentially harmful side effects. Using extremely sophisticated technologies, we have been able to demonstrate that the effectiveness of signaling and repair of DNA damage is highly dependent on these non-coding RNAs, each of which is generated from an individual lesion in the damaged genome and, therefore, is lesion-specific. Our challenge was to design an 'enlightened' therapeutic approach that does not affect the proteins that act in a generalized way, but instead targets the specific RNAs that accumulate at individual lesions, preventing the signaling and repair of the damaged DNA at very precise points within the genome, thereby blocking the proliferation and survival of the damaged tumor cell." IFOM researchers have developed an innovative class of molecules called 'antisense'. "These are – explains the first author of the study Flavia Michelini – oligonucleotides that have the extraordinary ability to bind a complementary RNA sequence and specifically inhibit the cell’s ability to repair their genome. In this way, the antisense molecules inhibit the signaling and repair of single DNA lesions without interfering with these cellular processes where it is undesirable."

It is an extremely sophisticated approach, analogous to the principles used in domotics: the nucleus of the cell is treated as a smart home, where you can control each single switch and turn it off selectively in the different rooms. Likewise, the antisense molecule can turn off the events involved in repairing DNA damage at precise genomic sites, without interfering elsewhere. "The antisense molecules - emphasizes d’Adda di Fagagna - constitute an emerging category of highly innovative drugs whose efficacy is dictated not just by their chemical properties but by their ability to selectively recognize the sequence of the RNA that we want to inhibit, and to bind to it."

It is a promising class of molecules in the context of personalization of therapy, working patient by patient and tumor by tumor, and paving the way for much more precise and less toxic medicine in the future.

The next step? "Currently – concludes d’Adda di Fagagna – we are studying the molecular and cellular biology of these mechanisms, but we are also projecting forward by trying to identify which classes of tumors preferentially accumulate damage at certain sites in the genome, so we can selectively target them with our approach. In exploring specific therapeutic applications, we will rely on strategic support by BiovelocITA, the first Italian accelerator dedicated to the biotech sector."

This research could not have been possible without the contribution of the European Commission (European Research Council advanced grant), AIRC, the EPIGEN project, and the collaboration of researchers from the University of Michigan and the Mechanobiology Institute in Singapore.

**Title:** Damage-induced lncRNAs control the DNA damage

response through interaction with DDRNAs at

individual double-strand breaks

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