# The artificial enzyme that "acts" natural

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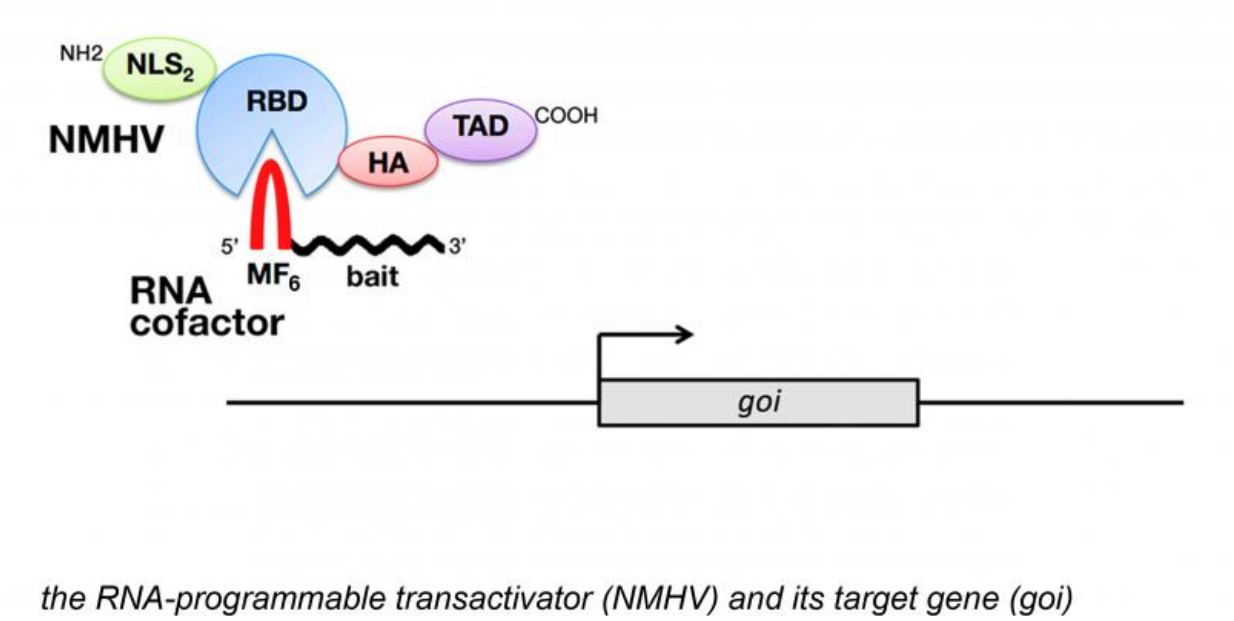


*the RNA-programmable transactivator (NMHV) and its target gene (goi)*

The RNA-programmable transactivator (NHMV) and its target gene (goi). Credit: SISSA

Certain genetic diseases arise from a deficit of specific genes. An enzyme that amplifies gene transcription could be a viable therapy in these cases, as long as genes are not stimulated to work on the wrong part of the body. SISSA scientists have created synthetic "intelligent" enzymes which are able to differentiate between active and inactive genes and selectively stimulate the former ones.

Every cell in the body (excepting gametes) contains the complete DNA of the individual it belongs to. Even so, a neuron in the brain differs completely from a liver cell— they perform specific functions and synthesize proteins in a completely different way. The reason for this is that within the DNA of each cell, some genes are either "on" or " off " depending on the requirements of the specific tissue they belong to. This means that when we want to stimulate genes to work harder to fight a genetic disease, for example , we need to target the appropriate tissue and not the entire body (doing so could cause serious damage ), which is anything but simple.

"We have created an enzyme that is able to 'see' the difference and act only where appropriate," says Prof. Antonello Mallamaci of the International School for Advanced Studies (SISSA) in Trieste, who led the recently-published study which can be found in the journal *Nucleic acid Research*. Mallamaci and Cristina Fimiani, a student at SISSA and first author of the article, created synthetic hybrid enzymes. "Hybrid" because , unlike classical transcription factors, which are made up almost entirely of proteins, these have a protein component , but they recognize the target gene via a dedicated RNA decoy, " explains Fimiani .

"An artificial RNA-programmable transcription factor was previously developed in other laboratories by domesticating the bacterial immune system. Ours are the first to be fully synthetic, even if their most important feature has nothing to do with this fact," notes Mallamaci. In fact, our enzymes do not stimulate gene transcription dramatically, but in a way comparable to endogenous regulators. "It may seem like a disadvantage at first, but it is their strength," says Fimiani. "Their work takes place within the natural physiological interval: they amplify the process in a limited way, and only if the gene is turned on. "In this way additional production of the protein can only occur in tissue where genes are active, even when the enzyme is administered to the entire organism .

"For this reason, our enzymes are excellent candidates for treating gene haploinsufficiencies," says Mallamaci . In the vast majority of cases , a healthy organism possesses two copies of each gene. Individuals with haploinsufficiency , however, are born with only one copy and this results in a production deficit of a given protein. This condition is the basis of some syndromes and neurological diseases." If we can stimulate the remaining gene to work harder, we can reduce the symptoms of the disease in some cases," says Fimiani .

"Hopefully our study will encourage others to repeat our research and confirm the results," says Mallamaci." Meanwhile, we are already working on improving our molecules and developing procedures for testing them in live animals ."

## More in detail

It was quality research that led to the publication of this study, highlighting the importance of training young researchers . Fimiani was a student at the University of Trieste when she began this study at SISSA for her dissertation. " The working hypothesis was unorthodox and the project was quite risky," says Mallamaci , also her thesis coordinator. "However , in the worst case scenario , her thesis work could have remained merely educational, allowing her to learn lab techniques necessary for all students in this field. "Fimiani was stubborn however, and eventually achieved impressive results despite some initial technical and scientific difficulties. Support from SISSA contributed to making it possible as well. Fimiani is continuing her studies as a graduate student at SISSA .

"All of this took place without specific funding for this research project, but rather through funds that SISSA invests in training students," says Mallamaci . "This means that outstanding students like Cristina can take advantage of opportunities here which can contribute to their academic

and professional future."

**More information:** "Upregulating endogenous genes by an RNA-programmable artificial transactivator," Cristina Fimiani, Elisa Goina and Antonello Mallamaci, *Nucl. Acids Res*. (2015), DOI: 10.1093/nar/gkv682

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